PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Donald L. MORTON

Serial No.: 09/751,373

Filed: December 29, 2000

For: PLURIPOTENT VACCINE AGAINST ENVELOPED VIRUSES

Group Art Unit: 1642

Examiner: A. Salimi

Atty. Dkt. No.: JWCI:011USC1

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37 C.F.R. §1.8

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Monica De La Paz
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BRIEF ON APPEAL

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BRIEF ON APPEAL

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Sir:

Appellants hereby submit an original and two copies of this Appeal Brief in response to the Final Office Action dated September 13, 2004. This Brief is filed pursuant to the Notice of Appeal mailed March 14, 2005. The due date for the Brief is June 17, 2005 in view of the enclosed Petition for Extension of Time and receipt of the Notice of Appeal by the Office on March 17, 2005 .

The fee for filing this Appeal Brief are attached. No additional fees are believed due in connection with this paper. However, should any other fees be due, or the attached fee be deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski L.L.P. Deposit Account No. 50-1212/JWCI:011USC1.

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I. REAL PARTY IN INTEREST

The real party in interest is the assignee, John Wayne Cancer Institute.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences.

III. STATUS OF THE CLAIMS

Claims 1-31 were filed with the original application. Claims 32-36 were added during prosecution. Of these, claims 2-6 and 21-31 have been previously canceled. Claims 11-17 and 34-36 were withdrawn from consideration as being drawn to a non-elected invention. The remaining claims (claims 1, 7-10, 18-20, and 32-33) are the subject of the present appeal.

IV. STATUS OF AMENDMENTS

In response to the final Office Action (dated September 13, 2004), Appellants submitted an Amendment to claim 1 to insert the word "distinct" before the phrase "common allotypes. Although Appellants disagreed with the Examiner's suggestion in the final Office Action about the need for this Amendment, this Amendment was nevertheless set forth by Appellants in the interest of advancing prosecution of the claims. In the Advisory Action dated March 25, 2005, Appellants were informed that the Amendment to claim 1 would not be entered because "the added limitation to main claim 1 requires further search, and also requires further consideration." Advisory Action, page 2. No other explanation was provided by the Examiner.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter pertains to compositions for the induction of immune responses against enveloped virus in mammals. Specification, page 2, lines 6-7. More particularly, the claimed subject matter generally pertains to compositions comprising major histocompatibility (MHC) antigens representing at least four common allotypes from a given mammalian species. See, *e.g.*, specification, page 11, lines 5-7. Exemplary allotypes are set forth throughout the specification, such as those set forth on page 12, lines 6-10 of the specification and in FIGS. 1-3.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 1, 7-10, 18-20, 32, and 33 are indefinite under 35 U.S.C. §112, second paragraph, for reciting the phrase "four common allotypes" and "composition comprising"

B. Whether claim 7 is indefinite under 35 U.S.C. §112, second paragraph, for reciting the phrase "antigens"

C. Whether claim 8 is indefinite under 35 U.S.C. §112, second paragraph, as being of improper dependent form for failing to limit the subject matter of a previous claim

D. Whether claim 10 is indefinite under 35 U.S.C. §112, second paragraph, for reciting the phrase "following human allotypes"

E. Whether there is adequate written description support for claims 1, 7-10, 18-20, 32, and 33 under 35 U.S.C. §112, first paragraph, in the specification

F. Whether claims 1, 7-10, 18-20, 32, and 33 are properly rejected under 35 U.S.C. §102(b) as being anticipated by Urban *et al.* (WO 94/04171; Exhibit 1)

G. Whether claims 1, 7-10 and 20 are properly rejected under 35 U.S.C. §102(b) as being anticipated by Stott *et al.* (WO 93/13126; Exhibit 2)

H. Whether claims 1, 7-10, and 20 are properly rejected under 35 U.S.C. §102(b) as being anticipated by Irie *et al.* (U.S. Patent 4,557,931; Exhibit 3)

I. Whether claims 1, 7-10, and 20 are properly rejected under 35 U.S.C. §102(e) as being anticipated by Peitropaolo *et al.* (U.S. Patent 5,891,437; Exhibit 4)

J. Whether claims 1, 7-10, 18-20 32, and 33 are properly rejected under 35 U.S.C. §102(b) as being anticipated by Ravindranath *et al.* (U.S. Patent 6,218,166 B1; Exhibit 5)

VII. ARGUMENT

A. Rejection of Claims 1, 7-10, 18-20, 32, and 33 Under 35 U.S.C. §112, Second Paragraph

1. The Language of Claim 1 is Sufficiently Clear and Definite

Claim 1 has been rejected as being vague and indefinite for reciting the terms "four common allotypes" and "antigens." Claim 1 recites "[a] composition comprising major histocompatibility (MHC) antigens representing at least four common allotypes from a given mammalian species." According to the Examiner, it is not clear what are the four common allotypes. Appellants respectfull traverse this rejection.

In reviewing a claim for compliance with 35 U.S.C. §112, second paragraph, the Examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope of the claimed invention and, therefore, serves the notice function required by 35 U.S.C. §112, second paragraph. See, *e.g.*, *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000).

a) *One of Ordinary Skill in the Art would Understand that the Phrase "four common allotypes" is Sufficiently Clear and Definite*

As an initial point, it should be noted that the Examiner has not provided any basis for why he finds the phrase "four common allotypes" objectionable. Other than stating "It is not clear," has provided no further analysis. It is unclear whether he finds the term "allotype" objectionable, or the phrase "common allotypes" objectionable. Appellants have addressed both these possibilities in their response, and have received no comment from the Examiner explaining why the rejection has been maintained.

One of ordinary skill in the art, when presented with the instant specification, would understand that the phrase "four common allotypes" is sufficiently clear and definite. As used in the context of claim 1, the term "allotype" refers to cell surface antigens "coded by diverse genes" that can "serve as targets for an alloimmune response" when perceived as foreign. See, *e.g.*, specification, page 24, lines 5-20, and in particular, lines 13-15 and lines 5-8. Examples of such antigens include MCH components (see, *e.g.*, specification, page 24, lines 13-20, and page 26, lines 19-20), ABO blood group antigens (specification, page 24, lines 13-15 and page 26, lines 19-20), and "other polymorphic antigens" (specification, page 24, lines 15-16). In the context of claim 1, which pertains to compositions comprising MHC antigens, the allotypes are MHC antigens. Page 25, lines 13-15 of the specification indicates that "[t]he MHC antigens that make up various allotypes are expressed on the surface of intact cells and are part of membrane preparations derived from cells expressing MHC antigens." Examples of MHC antigens include the HLA class I antigens and class II antigens, which are very familiar to those of ordinary skill in the art. See, *e.g.*, specification, page 24, lines 5-10 and page 25, lines 8-18. Numerous HLA

allotypes are set forth in the specification, such as in FIGS. 1-3, which provides lists of such allotypes.

Further, one of ordinary skill in the art, upon reading the specification, would understand that the phrase "four common allotypes" must refer to four separate and distinct MHC antigens. With regard to MHC antigens in particular, the specification provides that "by priming an individual to respond to ***foreign*** MHC antigens, it is believed that each enveloped virus particle or virus infected cell will be subject to a rapid and substantial immune response with activation of both the antibody mediated B cell and T cell arms of the immune response, and thereby prevent infection of host cells." Specification, page 25, lines 3-6. Further, the specification provides that "so long as ***more than one allotype is*** represented in the vaccine, the recipient of the vaccine will be immunized against at least one other allotype than his or her own." Specification, page 26, lines 13-15. Thus, in the context of claim 1, one of ordinary skill in the art, upon reading the specification, would have clearly understood that the phrase "four common allotypes" refers to four separate and distinct MHC antigens. No other interpretation is plausible in the context of the present invention. Had Appellants meant to claim compositions comprising a single allotype, then the claims would not have specified "four" common allotypes.

"Common" simply refers to those allotypes that are prevalent or regionally prevalent in a given mammalian species. See specification, page 26, lines 8-9. Examples of common allotypes are set forth in FIG. 1-FIG.3, which set forth a list of HLA allotypes and their frequency of distribution by ethnic group. For example, FIG. 3A-1 demonstrates that for North Africans (blacks), the four most common HLA A allotypes are A2 (13.6%), A23 (10.6%), A28 (11.9%), and A30 (9.3%). Thus, among North Africans (blacks), these allotypes are examples of "common" allotypes.

As noted in the specification, it is not necessary for the vaccine to represent all possible MHC allotypes. Specification, page 26, lines 7-8. Each individual has two allotypes. Thus, if a vaccine contains four common allotypes, the recipient of the vaccine will be immunized against at least one other allotype than his or her own." See Specification, page 26, lines 13-15. Thus, in order for a composition of matter to be comprised of four allotypes, it must include four or more cell surface antigens "coded by diverse genes" that can "serve as targets for an alloimmune response" when perceived as foreign. In the example set forth above pertaining to North Africans (blacks), a vaccine that includes the four most common HLA A allotypes set forth above would include "four common allotypes." Once again, the phrase "four common allotypes" implies that the antigens are distinct, one from another. Thus, one of ordinary skill in the art would be familiar with this terminology, and would understand that the phrase "four common allotypes" is sufficiently clear and definite.

b) One of Ordinary Skill in the Art would Understand that the Phrase "antigen" is Sufficiently Clear and Definite

The Examiner argues that the term "antigens" in claim 1 is objectionable because "the intended antigens are not defined." The language of claim 1 sets forth that the claimed composition comprises ***major histocompatibility antigens (MHC)*** that represent at least four common allotypes from a given mammalian species. Thus, on its face, the language of claim 1 makes it clear that the "antigens" are MHC antigens – in particular, those representing at least four common allotypes from a given mammalian species. The term "allotype" is discussed *supra*. Furthermore, term "antigen" is well-known in the art. As set forth above, MHC antigens are discussed throughout the specification. Further, MHC antigens are very well known to those of ordinary skill in the art.

The Examiner has failed to set forth analysis as to why he finds the term "antigens" objectionable has been set forth, other than to state that the "antigens" are not defined. It is respectfully submitted that the term "antigen" is sufficiently clear and definite to apprise one of ordinary skill in the art of the scope of the invention.

c) One of Ordinary Skill in the Art would Understand that the Phrase "composition comprising" is Sufficiently Clear and Definite

The Examiner also argues that for a "composition comprising," there must be more than one element. The claims are directed to ***a composition*** that comprises at least ***four common allotypes*** of a given species. As set forth above, the discussion of which is herein incorporated into this section, "allotypes" contemplates distinct allotypes. Thus, the claims compositions includes more than one element.

Further, the claimed compositions, by including the term "comprising," clearly contemplates the addition of agents other than "four common allotypes" in the composition. For example, the composition may include viral encoded antigens and/or adjuvants. See specification, page 25, lines 15-16. Certain specific additional agents are set forth in dependent claims (see, *e.g.*, claims 11-13, 16-17, and claim 20).

d) Conclusion

For each of the reasons set forth above, Appellants assert that the language of claim 1 is sufficiently clear and definite. It is therefore respectfully requested that the Board set aside the rejection of claim 1 under 35 U.S.C. §112, second paragraph.

2. *The Language of Claim 7 is Sufficiently Definite*

Claim 7 is said to be indefinite in not defining "antigens." Claim 7 recites "The composition of claim 1, wherein said antigens comprise both Class I and Class II antigens." Appellants assert that the term "antigen" in claim 7 is a MHC antigen. Claim 7 depends from claim 1, and claim 1 recites "A composition comprising ***major histocompatibility (MHC) antigens***." (emphasis added). As set forth above, the discussion of which is incorporated into this section, the term "antigens" is sufficiently clear and definite. Furthermore, as set forth above, one of ordinary skill in the art would be very familiar with MHC antigens and the term "antigen." Since the term "antigen" in claim 7 is sufficiently definite and descriptive to apprise one of ordinary skill of the scope of the claimed invention, the rejection is believed to be improper.

3. *The Language of Claim 8 is Sufficiently Definite*

Claim 8 is said to fail to limit the claim from which it depends. Appellants assert that this is absolutely false. Claim 1 require only four allotypes from a given species to be represented. In contrast, claim 8 required that ***all*** allotypes of a given mammalian species represented, which is much more restrictive, and thus more limiting.

The Examiner also argues that the phrase "all allotypes" is indefinite. The term "allotypes" has been discussed *supra*, the discussion of which is incorporated into this section. In the context of claim 8, "all allotypes" refers to the full spectrum of known MHC antigens from a given mammalian species. This is supported by page 25, line 20 through page 26, line 5, which provides that:

> In order for an effective MHC-based vaccine to protect an individual against all infecting virus particles, that vaccine must provide **the full spectrum of MHC antigens**. For humans, this would mean that a single vaccine would have to include sufficient allotypes of MHC antigens to guarantee that at least one of the

allotypes present on the virus envelope would be perceived as foreign by the vaccine recipient. (emphasis added).

Thus, one of ordinary skill in the art would understand that claim 8, with its recitation of "all allotypes," is sufficiently clear and definite. Thus, the rejection is believed to be improper.

4. The Language of Claim 10 is Sufficiently Definite

Claim 10 is said to be not only indefinite, but "incomprehensible" for use of the term "the following human allotypes" without any recitation of such. In response to the Office Action dated February 20, 2004, Appellants had corrected the erroneous omission of the list of allotypes, which had been included in originally filed claim 10, and pointed this out to the Examiner. The Examiner has made no further comment pertaining to this rejection, other than to indicate that the rejection has been maintained for the reason of record set forth in the Office Action. In view of the correction to claim 10, Appellants assume that this rejection has been overcome.

B. Rejection of Claims 1, 7-10, 18-20, 32, and 33 Under 35 U.S.C. §112, First Paragraph

Claims 1, 7-10, 18-20, 32 and 33 stand rejected under §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Action, the disclosure does not provide for a specific product isolated from a mammal in general or human in particular that can be administered to a suitable host. It is argued that no sequences are disclosed, and that the specification "does not set forth the metes and bounds of MHC antigens from all allotypes, polymorphic genes, *etc.*" Office Action dated Feb. 20, 2005, page 5. As a result, there is said to

not be enough information in the available literature to guide a person of ordinary skill in the art regarding undisclosed "antigens." Appellants respectfully traverse this rejection.

The Federal Circuit has stated that the test for the written description requirement is "whether the application relied upon 'reasonably conveys to the artisan that the inventor had possession of the claimed subject matter.'" *In re Daniels*, 144 F.3d 1452, 1456, 46 U.S.P.Q.2d 1788, 1790. See also *Markman v. Westview Instruments, Inc.* 52 F.3d 967, 34 USPQ 2d 1321 (Fed. Cir. 1995) (en banc) ("Claims must be read in view of the specification, of which they are a part.").

1. There is Sufficient Written Description Support in the Specification for Composition Claims

The Examiner's argues that "Applicant has only disclosed a general method of generating an anti-major histocompatability complex (MHC) immune response," and that the disclosure "does not provide for a specific product isolated from a mammal in general or human in particular that can be administered to a suitable host." These statement evince a complete lack of understanding of the invention and of the wealth of information provided in the instant specification.

Regarding the Examiner's comments that the specification only pertains to methods, Appellants point out that there is a substantial amount of information pertaining to compositions. The present invention derives from the inventors' observation that persons immunized with cells from other individuals appear to have an increased ability to fight off viral infections. Enveloped viruses, by definition, will carry allotypes of the individuals in which they were produced. Thus, the inventor determined that the allotypic antigens on the surface of enveloped viruses could be good targets for the host immune system, but only if that immune system was "primed" against those allotypes – something that does not happen naturally. Thus, a prime focus of the present

invention is directed to compositions of allotypes suitable for use in preparing vaccines directed against enveloped viruses. See entire specification, such as page 1, lines 6-11; page 10, lines 12-13; page 11, line 9 – page 12, line 22; page 25, line 20 – page 26, line 17; and Example 1.

2. *There is Sufficient Written Description Support in the Specification for Claims Directed to a Specific Product*

The Examiner's assertion that the specification "does not provide for a specific product isolated from a mammal in general or human in particular that can be administered to a suitable host" evinces a complete lack of understanding of the invention. As has been discussed *supra*, the discussion of which is herein incorporated into this section, the term "allotype" refers to cell surface antigens "coded by diverse genes" that can "serve as targets for an alloimmune response" when perceived as foreign. See, *e.g.*, specification, page 24, lines 5-20, and in particular, lines 13-15 and lines 5-8. In the context of claim 1, which pertains to compositions comprising MHC antigens, the allotypes are MHC antigens. Page 25, lines 13-15 of the specification indicates that "[t]he MHC antigens that make up various allotypes are epxressed on the surface of intact cells and are part of membrane preparations derived from cells expressing MHC antigens." Examples of MHC antigens include the HLA class I antigens and class II antigens, which are very familiar to those of ordinary skill in the art. See, *e.g.*, specification, page 24, lines 5-10 and page 25, lines 8-18. Numerous HLA allotypes are set forth in the specification, such as in FIGS. 1-3, which provides lists of such allotypes.

As discussed above, the specification provides a wealth of information regarding MHC allotypes that were known in the art at the time of filing. FIGS. 1-3 provide lists of HLA allotypes and their frequency distribution by ethnic group. Thus, the specification sets forth a

wealth of information pertaining to allotypes. One of ordinary skill in the art would have been very familiar with MHC allotypes, and the classes of MHC allotypes.

3. *Appellants are not Required to Recite Each and Every Known Allotype in their Specification*

The Examiner appears to be incorrectly arguing that Appellants must recite each and every known allotype in the specification. According to the Federal Circuit, "[i]t is well-established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of section 112." *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2D 1016, 1027 (Fed. Cir. 1991); *see also Utter v. Hiraga*, 856 F.2d 993, 998, 6 USPQ2D 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112, paragraph 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."). The specification satisfies the written description requirement because it reasonably conveys to one of skill in the art that they had possession of the claimed subject matter. *In re Daniels*, 144 F.3d 1452, 1456, 46 U.S.P.Q.2d 1788, 1790.

4. *The Examiner's Reliance on Regents of the University of California v. Eli Lilly & Co. is Misplaced*

The Action's reliance on *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997) is misplaced because this case is readily distinguishable. In *Regents of UC*, the patentee claimed a human insulin cDNA but had disclosed the sequence of only a rat insulin cDNA. It was evidence in that case that the patentee did not have a single sequence that qualified as a human insulin cDNA. In stark contrast, the present specification recites numerous antigens. The gene and protein sequences for many of the MHC antigens set forth in the specification were known at the time of filing, and in any event are

not the point of novelty for the present invention. Moreover, as discussed above, one need not even utilize purified proteins in order to practice the claimed invention. Thus, while facially addressing written description, the *Lilly* decision in no way argues against the patentability of the present invention.

5. *The Examiner has not Met his Burden in Rejecting a Claim Under the Written Description Requirement*

Appellants respectfully submit that without more analysis than he has set forth, the Examiner has not met his initial burden in rejecting a claim under the written description requirement of 35 U.S.C. §112, first paragraph. According to *In re Wertheim* (541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976)), the Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize in an Appellants' disclosure a description of the invention defined in the claims. No such reasons have been set forth. Rather, the few statements set forth by the Examiner evince no more than a complete misunderstanding of the claimed invention.

6. *Conclusion*

In summary, no information has been set forth by the Examiner that is sufficient to meet his initial burden in rejecting a claim under the written description requirement. In contrast, Appellants, have established that their disclosure is more than sufficient to satisfy the written description requirement. In view of the above, it is respectfully submitted that the Board withdraw the written description rejection of claims 1, 7-10, 18-20, 32 and 33 under 35 U.S.C. §112, first paragraph.

C. Rejection of Claims 1, 7-10, 18-20, 32, and 33 Under 35 U.S.C. §102

Claims 1, 7-10, 18-20, 32 and 33 stand rejected as anticipated under §102(b) by WO 94/04171 (Urban *et al;* Exhibit 1).

1. Urban et al. Fails to Anticipate the Claimed Invention

a) The Rejection Set forth by the Examiner is Not in Compliance with 37 C.F.R. §1.104(c)(2)

Appellants first note that the rejection is improper under 37 C.F.R. §1.104(c)(2). 37 C.F.R. §1.104(c)(2) recites:

> "In rejecting claims for want of novelty or for obviousness, the examiner must cite the best references at his or her command. When a reference is complex or shows or describes inventions other than that claimed by the applicant, the particular part relied on must be designated as nearly as practicable. ***The pertinence of each reference, if not apparent, must be clearly explained*** and each rejected claim specified." (emphasis added)

The Examiner, citing the abstract and claims 1-15, makes only a general allegation that the disclosed composition "appears to be identical or so similar that [it] is indistinguishable" from that which is now claimed. From these cited sections, the pertinence of the reference, and the Examiner has provided no explanation in the final Office Action or Advisory Action. Therefore, it is respectfully submitted that this rejection is improper.

b) Urban et al. Fails to Anticipate because it Fails to Expressly or Inherently Describe Compositions of MHC Allotypes

It is well-established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Urban *et al.* fails to anticipate because it does not disclose, either expressly or inherently, each and every limitation of the claimed invention. In particular, Urban *et al.* appears to Appellants to pertain to purified peptides that are capable of ***binding*** to MHC Class II allotypes. See, e.g., abstract and page 3, lines 19-22. Thus, these peptides are distinct from MHC antigens. Appellants find no indication that the peptides set forth in Urban *et al.* even represent an allotype itself. Moreover, as explained above, the discussion of which is herein incorporated into this section, the present invention requires presence of ***four common allotypes*** in a single composition. This is nowhere described in Urban *et al.* Thus, Urban *et al.* fails to anticipate.

The Examiner argues that in order to overcome Urban *et al.*, the claims at issue must recite "distinct allotype in a single composition." Appellants find this line of argumentation to be unclear. As set forth above, it appears to Appellants that Urban *et al.* is not even directed to composition comprising even a single allotype.

Perhaps the Examiner asserts that the claimed compositions can comprise a single agent (such as a single antigen). However, as set forth above, the discussion of which is incorporated into this section, the phrase "four common allotypes" must refer to four separate and distinct MHC antigens. The specification provides that "so long as ***more than one allotype is*** represented in the vaccine, the recipient of the vaccine will be immunized against at least one other allotype than his or her own." Specification, page 26, lines 13-15. Thus, in the context of claim 1, one of ordinary skill in the art, upon reading the specification, would have clearly understood that the phrase "four common allotypes" refers to four separate and distinct MHC allotypes. No other interpretation is plausible in the context of the present invention. Had Appellants meant to claim compositions comprising a single allotype, then the claims would not

specific "four" common allotypes. In any event, as to Urban *et al.*, this is a non-issue since Urban *et al.* does not even set forth compositions comprising a single MHC allotype.

The Examiner also incorrectly argues that "the burden is on the Applicant to show that the structure taught in the prior art is not capable of performing the intended use." This line of argumentation appears misplaced, and appears to be directed to method claims. However, the claims at issue are composition claims. Appellants are not claiming a new use - the claims are composition claims. Thus, this line of argumentation is not relevant.

c) Urban et al. Fails to Expressly or Inherently Set Forth Additional Limitations of Dependent Claims 7-8, 18-20, and 32-33

Regarding dependent claims, Urban *et al.* further fails to anticipate because it does not expressly or inherently set forth compositions comprising MHC class I and class II antigens (claim 7). Further, this references fails to set forth compositions comprising MHC antigens representative of all known allotypes of any mammalian species (claim 8). Appellants find no disclosure in Urban *et al.* pertaining to compositions of MHC antigens in intact cells (claim 33), in intact cells rendered incapable of growth (claim 18), or in cells that have been lethally irradiated (claim 19). Appellants also find no disclosure in Urban *et al.* pertaining to compositions of MHC allotypes that also include a pharmaceutically acceptable carrier, diluent, or excipient (claim 20), or compositions comprising at least four common MHC antigens wherein the antigens are provided in a cell free form (claim 32).

d) Conclusion

As set forth above, in order to anticipate, each limitation of the claimed invention must be expressly or inherently disclosed in the cited reference. Appellants, as discussed above, find

nothing in Urban *et al.* that either expressly or inherently sets forth a composition comprising at least four common allotypes from a given mammalian species.

In view of the above, Appellants therefore request that the Board withdraw the rejection of claims 1, 7-10, 18-20, 32 and 33 under 35 U.S.C. §102(b) based on Urban *et al.*.

2. Stott et al. Fails to Anticipate the Claimed Invention

Claims 1, 7-10, and 20 stand rejected as anticipated under §102(b) by WO 93/14126 (Stott *et al.*; Exhibit 2*)*.

a) The Rejection Set forth by the Examiner is Not in Compliance with 37 C.F.R. §1.104(c)(2)

Appellants first note that as with the previous rejection, this rejection is improper under 37 C.F.R. §1.104(c)(2). The Examiner, citing the abstract and claims 1-8, makes only a general allegation that the disclosed composition "appears to be identical or so similar that [it] is indistinguishable" from that which is now claimed. From these cited sections, the nature of the rejection is not apparent, and the Examiner has provided no explanation. Therefore, this rejection is improper.

b) Stott et al. Fails to Anticipate because it Fails to Expressly or Inherently Describe Compositions Comprising at Least Four MHC Allotypes

Nevertheless, Stott *et al.* fails to anticipate because it does not disclose, either expressly or inherently, each and every limitation of the claimed invention. In particular, Stott *et al.* does not teach a composition comprising MHC antigens representing at least ***four*** common allotypes from a given mammalian species. Stott *et al.* recites "a major histocompatibility complex class II antigen", and does not appear to Appellants to pertain to compositions comprising ***at least four*** common MHC allotypes. As explained above, the discussion of which is incorporated into this

section, the compositions of the present invention require presence of at least four distinct allotypes. Appellants have not been able to identify any such disclosure in Stott *et al.* Thus, Stott *et al.* fails to anticipate the claimed invention.

The Examiner argues incorrectly argues that in order to overcome Stott *et al.*, the claims at issue must recite "distinct allotype in a single composition." This is incorrect. As set forth above, in order to anticipate, each limitation of the claimed invention must be expressly or inherently disclosed in the cited reference. Appellants, as discussed above, find nothing in Stott *et al.* that either expressly or inherently sets forth a composition comprising at least four common allotypes from a given mammalian species.

As set forth above, the discussion of which is incorporated into this section, one of ordinary skill in the art would understand that "four common allotypes," as used herein, contemplates distinct MHC antigens rather than a single antigen. As set forth above, with regard to MHC antigens in particular, the specification provides that "by priming an individual to respond to ***foreign*** MHC antigens, it is believed that each enveloped virus particle or virus infected cell will be subject to a rapid and substantial immune response with activation of both the antibody mediated B cell and T cell arms of the immune response, and thereby prevent infection of host cells." Specification, page 25, lines 3-6. Further, the specification provides that "so long as ***more than one allotype is*** represented in the vaccine, the recipient of the vaccine will be immunized against at least one other allotype than his or her own." Specification, page 26, lines 13-15. Thus, in the context of claim 1, one of ordinary skill in the art, upon reading the specification, would have clearly understood that the phrase "four common allotypes" refers to four separate and distinct MHC antigens from different individuals. As previously discussed, no other interpretation is plausible in the context of the present invention. Had Appellants meant to

claim compositions comprising only a single allotype, then the claims would not have specified "four."

The Examiner, in repeating the arguments set forth in the prior rejection, argues that "the burden is on the Applicant to show that the structure taught in the prior art is not capable of performing the intended use." This line of argumentation appears misplaced, and appears to be directed to method claims. However, the claims at issue are composition claims. Thus, this line of argumentation is not relevant.

c) Stott et al. Fails to Expressly or Inherently Set Forth Additional Limitations of Dependent Claims 7-8

Regarding dependent claims, Stott *et al.* further fails to anticipate because it does not expressly or inherently set forth compositions comprising both MHC class I and class II antigens (claim 7). Further, this references fails to set forth compositions comprising MHC antigens representative of all known allotypes of any mammalian species (claim 8).

d) Conclusion

In view of the above, Appellants therefore request that the Board withdraw the rejection of claims 1, 7-10, and 20 under 35 U.S.C. §102(b) based on Stott *et al.*

3. Irie et al. Fails to Anticipate the Claimed Invention

Claims 1, 7-10, and 20 stand rejected as anticipated under §102(b) by U.S. Patent 4,557,931 (Irie *et al.*).

a) The Rejection Set forth by the Examiner is Not in Compliance with 37 C.F.R. §1.104(c)(2)

Appellants first note that as with the previous rejection, this rejection is improper under 37 C.F.R. §1.104(c)(2). The Examiner, citing only claims 1-4, makes only a general allegation

that the disclosed composition "appears to be identical or so similar that [it] is indistinguishable" from that which is now claimed. From these cited claims, the nature of the rejection is not apparent, and the Examiner has provided no explanation other than to suggest that it appears that the same composition is being claims. Therefore, it is respectfully submitted that this rejection is improper.

b) Irie et al. Fails to Anticipate because it Fails to Expressly or Inherently Describe Compositions Comprising at Least Four MHC Allotypes

Irie *et al.* fails to anticipate because it does not disclose, either expressly or inherently, each and every limitation of the claimed invention. In particular, Irie *et al.* does not teach a composition comprising MHC antigens representing at least four common allotypes from a given mammalian species. Irie *et al.* appears to Appellants to pertain to antigenic conjugates of GM2 oligosaccharies and a protein carrier. GM2 is not a MHC antigen. In addition, Appellants find no disclosure in Irie *et al.* pertaining to MHC antigens as the protein carrier. Possible carriers set forth include human serum albumin and other "nontoxic" carriers. See column 5, lines 25-28. Thus, Irie *et al.* does not appear relevant in any respect to the claimed invention. Since Irie *et al.* does not expressly or inherently set forth each limitation of the claimed invention, it fails to anticipate.

The Examiner argues that in order to overcome Irie *et al.*, the claims at issue must recite "distinct allotype in a single composition." This is incorrect. As set forth above, in order to anticipate, each limitation of the claimed invention must be expressly or inherently disclosed in the cited reference. Appellants, as discussed above, find nothing in Irie *et al.* that either expressly or inherently sets forth a composition comprising at least four common allotypes from a given mammalian species. As set forth above, "allotypes" contemplates distinct antigens. The

discussion above pertaining to "four common allotypes," herein incorporated into this section, clearly contemplates such an interpretation of allotypes.

The Examiner also incorrectly argues that "the burden is on the Applicant to show that the structure taught in the prior art is not capable of performing the intended use." This line of argumentation appears misplaced, and appears to be directed to method claims. However, the claims at issue are composition claims. Thus, this line of argumentation is not relevant.

c) Irie et al. Fails to Expressly or Inherently Set Forth Additional Limitations of Dependent Claims 7-8, 18-20, and 32-33

Regarding dependent claims, Irie *et al.* further fails to anticipate because it does not expressly or inherently set forth compositions comprising MHC class I and class II antigens (claim 7). Further, this references fails to set forth compositions comprising MHC antigens representative of all known allotypes of any mammalian species (claim 8). Appellants find no disclosure in Irie *et al.* pertaining to compositions of MHC antigens in intact cells (claim 33), in intact cells rendered incapable of growth (claim 18), or in cells that have been lethally irradiated (claim 19). Appellants also find no disclosure in Irie *et al.* pertaining to compositions of MHC allotypes that also include a pharmaceutically acceptable carrier, diluent, or excipient (claim 20), or compositions comprising at least four common MHC antigens wherein the antigens are provided in a cell free form (claim 32).

d) Conclusion

In view of the above, Appellants therefore request that the Board withdraw the rejection of claims 1, 7-10, and 20 under 35 U.S.C. §102(b) based on Irie *et al.*.

4. *Pietropaolo et al. Fails to Anticipate because it Fails to Expressly or Inherently Describe each Limitation of the Claimed Invention*

Claims 1, 7-10, and 20 stand rejected as anticipated under §102(e) by U.S. Patent 5,891,437 to Pietropaolo *et al.*

a) *The Rejection Set forth by the Examiner is Not in Compliance with 37 C.F.R. §1.104(c)(2)*

Appellants first note that as with the previous rejection, this rejection is improper under 37 C.F.R. §1.104(c)(2). The Examiner, citing only claims 1-16, makes only a general allegation that the disclosed composition "appears to be identical or so similar that [it] is indistinguishable" from that which is now claimed. From these cited claims, the nature of the rejection is not apparent, and the Examiner has provided no explanation other than to suggest that it appears that the same composition is being claims. Therefore, it is respectfully submitted that this rejection is improper.

b) *Peitropaolo et al. Fails to Anticipate because it Fails to Expressly or Inherently Describe Compositions Comprising at Least Four MHC Allotypes*

Nevertheless, Pietropaolo *et al.* fails to anticipate because it does not disclose, either expressly or inherently, each and every limitation of the claimed invention. In particular, Pietropaolo *et al.* does not teach a composition comprising MHC antigens representing at least four common allotypes from a given mammalian species. Pietropaolo *et al.* appears to Appellants to pertain to a PM-1 protein or an epitope thereof. There is no indication from Peitropaolo *et al.* that PM-1 is an MHC antigen. It is said to be expressed in pancreatic islet cells and a human insulinoma (see abstract). Thus, Pietropaolo *et al.* does not appear to Appellants to be relevant to the claimed invention, as it does not even pertain to MHC antigens. This is no where described in Pietropaolo *et al.* Since Pietropaolo *et al.* does not expressly or inherently set forth each limitation of the claimed invention, it cannot anticipate.

The Examiner argues incorrectly argues that in order to overcome Pietropaolo *et al.*, the claims at issue must recite "distinct allotype in a single composition." This is incorrect. As set forth above, in order to anticipate, each limitation of the claimed invention must be expressly or inherently disclosed in the cited reference. Appellants, as discussed above, find nothing in Pietropaolo *et al.* that either expressly or inherently sets forth a composition comprising at least four common allotypes from a given mammalian species. As set forth above, "allotypes" contemplates distinct allotypes. The discussion set forth above pertaining to written description support for "allotypes," which provides supportive evidence from the specification that "four common allotypes" contemplates four distinct allotypes, is herein incorporated into this section.

The Examiner also incorrectly argues that "the burden is on the Applicant to show that the structure taught in the prior art is not capable of performing the intended use." This line of argumentation again appears out of place, and appears to be directed to method claims. No method claims are at issue. Thus, this line of argumentation is not relevant.

c) Pietropaolo et al. Fails to Expressly or Inherently Set Forth Additional Limitations of Dependent Claims 7-8, 18-20, and 32-33

Regarding dependent claims, Pietropaolo *et al.* further fails to anticipate because it does not expressly or inherently set forth compositions comprising MHC class I and class II antigens (claim 7). Further, this references fails to set forth compositions comprising MHC antigens representative of all known allotypes of any mammalian species (claim 8). Appellants find no disclosure in Pietropaolo *et al.* pertaining to compositions of MHC antigens in intact cells (claim 33), in intact cells rendered incapable of growth (claim 18), or in cells that have been lethally irradiated (claim 19). Appellants also find no disclosure in Pietropaolo *et al.* pertaining to compositions of MHC allotypes that also include a pharmaceutically acceptable carrier, diluent,

or excipient (claim 20), or compositions comprising at least four common MHC antigens wherein the antigens are provided in a cell free form (claim 32).

d) Conclusion

In view of the above, Appellants therefore request that the Board withdraw the rejection of claims 1, 7-10, and 20 under 35 U.S.C. §102(e) based on Pietropaolo *et al.*

5. Ravindranath et al. Fails to Anticipate because it Fails to Expressly or Inherently Describe each Limitation of the Claimed Invention

Claims 1, 7-10, 18-20, 32 and 33 stand rejected as anticipated under §102(e) by U.S. Patent 6,218,166 (Ravindranath *et al.*).

a) The Rejection Set forth by the Examiner is Not in Compliance with 37 C.F.R. §1.104(c)(2)

Appellants first note that as with the previous rejection, this rejection is improper under 37 C.F.R. §1.104(c)(2). The Examiner, citing the abstract and claims 1-30, makes only a general allegation that the disclosed composition "appears to be identical or so similar that [it] is indistinguishable" from that which is now claimed. From these cited claims, the nature of the rejection is not apparent, and the Examiner has provided no explanation other than to suggest that it appears that the same composition is being claims. Therefore, it is respectfully submitted that this rejection is improper.

b) Ravindranath et al. Fails to Anticipate because it Fails to Expressly or Inherently Describe Compositions Comprising at Least Four MHC Allotypes

Nevertheless, Ravindranath *et al.* fails to anticipate because it does not disclose, either expressly or inherently, each and every limitation of the claimed invention. Other than claim 19, the compositions described are drawn to a single cell. As explained above, the discussion of which is herein incorporated into this section, the phrase "four common allotypes" contemplates

antigenic material more than one individual. A single cell cannot have four allotypes. With regard to claim 19, there is nothing in Ravindranath *et al.* that expressly or inherently sets forth combining multiple cells, each with different allotypes. Since Ravindranath *et al.* does not expressly or inherently set forth each limitation of the claimed invention, it cannot anticipate.

The Examiner argues incorrectly argues that in order to overcome Ravindranath *et al.*, the claims at issue must recite "distinct allotype in a single composition." This is incorrect. As set forth above, in order to anticipate, each limitation of the claimed invention must be expressly or inherently disclosed in the cited reference. Appellants, as discussed above, find nothing in Ravindranath *et al.* that either expressly or inherently sets forth a composition comprising at least four common allotypes from a given mammalian species. As set forth above, "allotypes" contemplates distinct allotypes, and not four identical allotypes.

The Examiner also incorrectly argues that "the burden is on the Applicant to show that the structure taught in the prior art is not capable of performing the intended use." Once again, this line of argumentation appears misplaced, and appears to be directed to method claims. As with the above rejections, the claims at issue are composition claims. Thus, this line of argumentation is misplaced.

In view of the above, Appellants therefore request that the Board withdraw the rejection of claims 1, 7-10, 18-20, 32, and 33 under 35 U.S.C. §102(e) based on Ravindranath *et al.*

VIII. CONCLUSION

It is respectfully submitted, in light of the above, that none of the pending claims are properly rejected under 35 U.S.C. §112, first or second paragraph or 35 U.S.C. §102. Reversal of the pending grounds for rejection is thus respectfully requested.

Respectfully submitted,

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Date: June 17, 2005

CLAIMS APPENDIX

1. (Previously presented) A composition comprising major histocompatibility (MHC) antigens representing at least four common allotypes from a given mammalian species.

7. (Previously presented) The composition of claim 1, wherein said antigens comprise both Class I and Class II antigens.

8. (Previously presented) The composition of claim 1, wherein said composition comprises MHC antigens representative of all known allotypes of said mammalian species.

9. (Original) The composition of claim 1, wherein said mammal is a human.

10. (Previously presented) The composition of claim 9, wherein said allotypes include at least one of the following human allotypes:

$HLAA_1$, A_2, A_3, A_{11}, A_{24}, A_{29}, A_{32},

B_7, B_8, B_{13}, B_{35}, B_{38}, B_{44}, B_{55}, B_{60}, B_{62},

CW_1, CW_2, CW_4, CW_5, CW_6, CW_7, CW_9, CW_{10}, CW_{11},

DR_1, DR_3, DR_4, DR_7, DR_8, DR_{11}, DR_{12}, DR_{13}, DR_{15},

ABO Blood Groups.

18. (Previously presented) The composition of claim 33, wherein said cells are rendered incapable of growth.

19. (Original) The composition of claim 18, wherein said cells are lethally irradiated.

20. (Original) The composition of claim 1, further comprising a pharmaceutically acceptable carrier, diluent or excipient.

32. (Previously presented) The composition of claim 1, wherein said MHC antigens are provided in a cell free form.

33. (Previously presented) The composition of claim 1, wherein said MHC antigens are provided in intact cells.

EVIDENCE APPENDIX

Exhibit 1. Urban *et al.* (WO 94/04171); cited in Office Action dated February 20, 2004.

Exhibit 2. Stott *et al.* (WO 93/14126); cited in Office Action dated February 20, 2004.

Exhibit 3. Irie *et al.* (U.S. Patent 4,557,931); cited in Office Action dated February 20, 2004.

Exhibit 4. Peitropaolo *et al.* (U.S. Patent 5,891,437); cited in Office Action dated February 20, 2004.

Exhibit 5. Ravindranath *et al.* (U.S. Patent 6,218,166 B1); cited in Office Action dated February 20, 2004.

EXHIBIT 1

CORRECTED VERSION*

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 37/00, 37/02, 37/22
A61K 31/70, C07K 7/00, 7/08
C07K 7/10, C07H 17/00

A1

(11) International Publication Number: WO 94/04171

(43) International Publication Date: 3 March 1994 (03.03.94)

(21) International Application Number: PCT/US93/07545

(22) International Filing Date: 11 August 1993 (11.08.93)

(30) Priority data:

07/925,460	11 August 1992 (11.08.92)	US
Not furnished	15 June 1993 (15.06.93)	US

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(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: IMMUNOMODULATORY PEPTIDES

(57) Abstract

A purified preparation of a peptide consisting essentially of an amino acid sequence identical to that of a segment of a naturally-occurring human protein, said segment being of 10 to 30 residues in length, inclusive, wherein said peptide binds to a human major histocompatibility complex (MHC) class II allotype.

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IMMUNOMODULATORY PEPTIDES

This application is a continuation-in-part of co-pending USSN 07/925,460, filed August 11, 1992. The invention was made in the course of research funded in part by the U.S. Government under NIH Grant 5R35-CA47554; the U.S. Government therefore has certain rights in the invention.

The field of the invention is major histocompatibility complex (MHC) antigens.

Background of the Invention

Major histocompatibility complex (MHC) class II antigens are cell surface receptors that orchestrate all specific immune responses in vertebrates. Humans possess three distinct MHC class II isotypes: DR, for which approximately 70 different allotypes are known; DQ, for which 33 different allotypes are known; and DP, for which 47 different allotypes are known. Each individual bears two to four DR alleles, two DQ alleles, and two DP alleles.

MHC receptors (both class I and class II) participate in the obligate first step of immune recognition by binding small protein fragments (peptides) derived from pathogens or other non-host sources, and presenting these peptides to the regulatory cells (T cells) of the immune system. In the absence of MHC presentation, T cells are incapable of recognizing pathogenic material. Cells that express MHC class II receptors are termed antigen presenting cells (APC). APCs ingest pathogenic organisms and other foreign materials by enveloping them in endosomic vesicles, then subjecting them to enzymatic and chemical degradation. Foreign proteins which are ingested by APCs are partially degraded or "processed" to yield a mixture of peptides, some of which are bound by MHC class II molecules that

are *en route* to the surface. Once on the cell surface, MHC-bound peptides are available for T cell recognition.

MHC class II antigens are expressed on the surface of APCs as a trimolecular complex composed of an α chain, a β chain, and a processed peptide. Like most polypeptides that are expressed on the cell surface, both α and β chains contain short signal sequences at their NH_2 termini which target them to the endoplasmic reticulum (ER). Within the ER the class II α/β chain complex associates with an additional protein termed the invariant chain (Ii). Association with Ii is proposed to block the premature acquisition of peptides (by blocking the peptide binding cleft of the MHC heterodimer), promote stable α/β interaction, and direct subsequent intracellular trafficking of the complex to endosomal vesicles. In the endosomes, Ii is removed by a process involving proteolysis; this exposes the peptide binding cleft, thus allowing peptides present in the endosome to bind to the MHC molecule. The class II/ peptide complex is transported from the endosomes to the cell surface where it becomes accessible to T-cell recognition and subsequent activation of immune responses. Class II MHC molecules bind not only to peptides derived from exogenous (ingested) proteins, but also to those produced by degradation of endogenous (self) proteins. The amount of each species of peptide which binds class II is determined by its local concentration and its relative binding affinity for the given class II binding groove, with the various allotypes displaying different peptide-binding specificities.

Early during fetal development, the mammalian immune system is "tolerized", or taught not to react, to self-peptides. The stability and maintenance of this system is critical for ensuring that an animal does not generate an immune response against self. A breakdown of

this system gives rise to autoimmune conditions such as diabetes, rheumatoid arthritis and multiple sclerosis. Current technologies intended to manipulate the immune system into reestablishing proper nonresponsiveness include protocols involving the intravenous delivery of synthetic, high affinity binding peptides as blocking peptides.

Vaccination can generate protective immunity against a pathogenic organism by stimulating an antibody-mediated and/or a T cell-mediated response. Most of the current vaccination strategies still use relatively crude preparations, such as attenuated or inactivated viruses. These vaccines often generate both antibody- and cell-mediated immunity, and do not allow one to modulate the type of immune response generated. Moreover, in many diseases the generation of the wrong type of response can result in an exacerbated disease state.

Summary of the Invention

In the work disclosed herein, naturally processed peptides bound to six of the some 70 known human MHC class II DR allotypes (HLA-DR1, HLA-DR2, HLA-DR3, HLA-DR4, HLA-DR7, and HLA-DR8) have been characterized. These peptides were found to be predominantly derived from self proteins rather than foreign proteins. Several self peptide families have been identified with the unexpected property of degenerate binding: that is, a given self-peptide will bind to a number of HLA-DR allotypes. This observation runs counter to the widely-accepted view of MHC class II function, which dictates that each allotype binds a different set of peptides. Furthermore, many if not all of the self-peptides disclosed herein bind to the class II molecules with relatively high affinity. These three characteristics--(1) self rather than foreign, (2) degeneracy, and (3)

high affinity binding--suggest a novel means for therapeutic intervention in disease conditions characterized by autoreactivity, such as Type I diabetes, rheumatoid arthritis, and multiple sclerosis. In addition, such therapy could be used to reduce transplant rejection.

In the therapeutic methods of the invention, short peptides modelled on the high-affinity immunomodulating self peptides of the invention (which preferably are nonallelically restricted) are introduced into the APCs of a patient. Tissue typing to determine the particular class II alleles expressed by the patient may be unnecessary, as the peptides of the invention are bound by multiple class II isotypes. It may be useful to employ a "cocktail" of peptides, where complete degeneracy is lacking for individual peptides, i.e., where peptides binds to fewer than all allotypes; the cocktail provides overlapping binding specificity. Once in the APC, a peptide binds to the class II molecules with high affinity, thereby blocking the binding of immunogenic peptides which are responsible for the immune reaction characteristic of the disease condition. Because the blocking peptides of the invention are self peptides with the exact carboxy and amino termini tolerized during ontogeny, they are immunologically inert and will not induce an immune response which may complicate treatment using non-self blocking peptides.

The peptides of the invention may be introduced into APCs directly, e.g., by intravenous injection of a solution containing one or more of the peptides. Alternatively, the APCs may be provided with a means of synthesizing large quantities of the blocking peptides intracellularly. Recombinant genes that encode ER and/or endosomal targeting signals fused to blocking peptide sequences are linked to appropriate expression control

sequences and introduced into APCs. Once in the cell, these genes direct the expression of the hybrid peptides. Peptides targeted to the ER will bind class II α and β chains as they are translated and assembled into heterodimers. The presence of high affinity binding peptides within the ER will prevent association of the α/β complex with invariant chain, and thus interfere with intracellular trafficking. The class II molecule/ blocking peptide complex may subsequently be expressed on the cell surface, but would not elicit an immune response since T cells are tolerized to this complex early in development. The use of peptides tagged with ER retention signals may also prevent the peptide-complexed class II molecules from leaving the ER. Alternatively, the recombinant peptide may be tagged with an endosomal targeting signal which directs it to the endosomal compartment after synthesis, thereby also skewing the ratio of endogenously-processed peptide to blocking peptide in the endosome and favoring binding of the high affinity blocking peptide to any class II molecules which did not bind it in the ER. It may be advantageous, for any individual patient, to employ one or more ER-directed peptides in combination with one or more endosome-directed peptide, so that α-β complexes which are not filled in the ER with peptides of the invention are then blocked in the endocytic pathway. The end result again is cell surface expression of a non-immunogenic class II/peptide complex.

The use of a class II nonrestricted high affinity binding peptide coupled to an intracellular delivery system permits the specific down-regulation of class II restricted immune responses without invoking the pleiotropic adverse reactions associated with the current pharmacological strategies. Successful application of these technologies will constitute a significant advance

towards the treatment of autoimmune disease and prevention of transplant rejection.

The intracellular delivery system of the invention can also be utilized in a novel method of vaccination of an animal, e.g., a human patient or a commercially significant mammal such as a cow which is susceptible to diseases such as hoof and mouth disease. Such a system can be tailored to generate the type of immune response required in a given situation by adjustments in the following: (a) peptide specificity for class I or class II MHC; (b) peptide/protein length and/or sequence, and (c) using specific tags for organelle targeting. The system of the invention ensures that peptides are produced only within cells, and are not present outside the cells where they could stimulate antibody production by contact with B cells. This limits the immune response generated by such a vaccine to T cell-mediated immunity, thereby preventing either an inappropriate or potentially deleterious response as might be observed with standard vaccines targeting the organisms which cause, for example, HIV, malaria, leprosy, and leishmaniasis. Furthermore, this exclusively T cell-mediated immune response can be class I or class II-based, or both, depending upon the length and character of the immunogenic peptides: MHC class I molecules are known to bind preferentially to peptides 8 to 10 residues in length, while class II molecules bind with high affinity to peptides that range from 12 to 25 residues long.

Immunization and therapy according to the invention can employ a purified preparation of a peptide of the invention, i.e., a peptide which includes an amino acid sequence identical to that of a segment of a naturally-occurring human protein (i.e., a "self protein"), such segment being of 10 to 30 residues in length, wherein the peptide binds to a human MHC class II

allotype, and preferably binds to at least two distinct MHC class II allotypes (e.g., any of the approximately 70 known DR allotypes, approximately 47 known DP allotypes, or approximately 33 known DQ allotypes). The portion of the peptide corresponding to the self protein segment is herein termed a "self peptide". By "purified preparation" is meant a preparation at least 50% (by weight) of the polypeptide constituents of which consists of the peptide of the invention. In preferred embodiments, the peptide of the invention constitutes at least 60% (more preferably at least 80%) of the purified preparation. The naturally-occurring human protein is preferably HLA-A2 (as broadly defined below), HLA-A29, HLA-A30, HLA-B44, HLA-B51, HLA-Bw62, HLA-C, HLA-DP β-chain, HLA-DQ α-chain, HLA-DQ β-chain, HLA-DQ3.2 β-chain, HLA-DR α-chain, HLA-DR β-chain, HLA-DR4 β-chain, invariant chain (Ii), Ig kappa chain, Ig kappa chain C region, Ig heavy chain, Na^+/K^+ ATPase, potassium channel protein, sodium channel protein, calcium release channel protein, complement C9, glucose-transport protein, CD35, CD45, CD75, vinculin, calgranulin B, kinase C ζ-chain, integrin β-4 gp150, hemoglobin, tubulin α-1 chain, myosin β-heavy chain, α-enolase, transferrin, transferrin receptor, fibronectin receptor α-chain, acetylcholine receptor, interleukin-8 receptor, interferon α-receptor, interferon γ-receptor, calcitonin receptor, LAM (lymphocyte activation marker) Blast-1, LAR (leukocyte antigen-related) protein, LIF (leukemia inhibitory factor) receptor, 4F2 cell-surface antigen (a cell-surface antigen involved in normal and neoplastic growth) heavy chain, cystatin SN, VLA-4 (a cell surface heterodimer in the integrin superfamily of adhesion receptors), PAI-1 (plasminogen activator inhibitor-1), IP-30 (interferon-γ induced protein), ICAM-2, carboxypeptidase E, thromboxane-A synthase, NADH-

cytochrome-b5 reductase, c-myc transforming protein, K-ras transforming protein, MET kinase-related transforming protein, interferon-induced guanylate-binding protein, mannose-binding protein, apolipoprotein B-100, cathepsin C, cathepsin E, cathepsin S, Factor VIII, von Willebrand factor, metalloproteinase inhibitor 1 precursor, metalloproteinase inhibitor 2, plasminogen activator inhibitor-1, or heat shock cognate 71 kD protein; it may be an MHC class I or II antigen protein or any other human protein which occurs at the cell surface of APCs. The self peptide preferably conforms to the following motif: at a first reference position (I) at or within 12 residues of the amino terminal residue of the segment, a positively charged residue (i.e., Lys, Arg, or His) or a large hydrophobic residue (i.e., Phe, Trp, Leu, Ile, Met, Tyr, or Pro; and at position I+5, a hydrogen bond donor residue (i.e., Tyr, Asn, Gln, Cys, Asp, Glu, Arg, Ser, Trp, or Thr). In addition, the peptide may also be characterized as having, at positions I+9, I+1, and/or I-1, a hydrophobic residue (i.e., Phe, Trp, Leu, Ile, Met, Pro, Ala, Val, or Tyr) (+ denotes positions to the right, or toward the carboxy terminus, and - denotes positions to the left, or toward the amino terminus.) A typical peptide of the invention will include a sequence corresponding to residues 31-40 (i.e., TQFVRFDSDA; SEQ ID NO: 149) or residues 106-115 (i.e., DWRFLRGYHQ; SEQ ID NO: 150) of HLA-A2, or residues 107-116 (i.e., RMATPLLMQA; SEQ ID NO: 151) of Ii, or a sequence essentially identical to any one of the sequences set forth in Tables 1-10 below.

The therapeutic and immunization methods of the invention can also employ a nucleic acid molecule (RNA or DNA) encoding a peptide of the invention, but encoding less than all of the entire sequence of the self protein. The nucleic acid preferably encodes no substantial

portion of the self protein other than the specified self peptide which binds to a MHC class II molecule, although it may optionally include a signal peptide or other trafficking sequence which was derived from the self protein (or from another protein). A trafficking sequence is an amino acid sequence which functions to control intracellular trafficking (directed movement from organelle to organelle or to the cell surface) of a polypeptide to which it is attached. Such trafficking sequences might traffic the polypeptide to ER, a lysosome, or an endosome, and include signal peptides (the amino terminal sequences which direct proteins into the ER during translation), ER retention peptides such as KDEL (SEQ ID NO: 152); and lysosome-targeting peptides such as KFERQ (SEQ ID NO: 153), QREFK (SEQ ID NO: 154), and other pentapeptides having Q flanked on one side by four residues selected from K, R, D, E, F, I, V, and L. An example of a signal peptide that is useful in the invention is a signal peptide substantially identical to that of an MHC subunit such as class II α or β; e.g., the signal peptide of MHC class II α is contained in the sequence MAISGVPVLGFFIIAVLMSAQESWA (SEQ ID NO: 155). The signal peptide encoded by the nucleic acid of the invention may include only a portion (e.g., at least ten amino acid residues) of the specified 25 residue sequence, provided that portion is sufficient to cause trafficking of the polypeptide to the ER. In preferred embodiments, the nucleic acid of the invention encodes a second self peptide and a second trafficking sequence (which may be identical to or different than the first self peptide and first trafficking sequence), and it may encode additional self peptides and trafficking sequences as well. In still another variation on this aspect of the invention, the self peptide sequence (or a plurality of self peptide sequences arranged in tandem) is linked

by a peptide bond to a substantially intact Ii polypeptide, which then carries the self peptide sequence along as it traffics the class II molecule from ER to endosome.

The nucleic acid of the invention may also contain expression control sequences (defined as transcription and translation start signals, promoters, and enhancers which permit and/or optimize expression of the coding sequence with which they are associated) and/or genomic nucleic acid of a phage or a virus, such as an attenuated or non-replicative, non-virulent form of vaccinia virus, adenovirus, Epstein-Barr virus, or a retrovirus.

The peptides and nucleic acids of the invention may be prepared for therapeutic use by suspending them directly in a pharmaceutically acceptable carrier, or by encapsulating them in liposomes, immune-stimulating complexes (ISCOMS), or the like. Such preparations are useful for inhibiting an immune response in a human patient, by contacting a plurality of the patient's APCs with the therapeutic preparation and thereby introducing the peptide or nucleic acid into the APCs.

Also within the invention is a cell (e.g., a tissue culture cell or a cell, such as a B cell or APC, within a human) containing the nucleic acid molecule of the invention. A cultured cell containing the nucleic acid of the invention may be used to manufacture the peptide of the invention, in a method which involves culturing the cell under conditions permitting expression of the peptide from the nucleic acid molecule.

Disclosed herein is a method of identifying a nonallelically restricted immunomodulating peptide, which method includes the steps of:

(a) fractionating a mixture of peptides eluted from a first MHC class II allotype;

(b) identifying a self peptide from this mixture; and

(c) testing whether the self peptide binds to a second MHC class II allotype, such binding being an indication that the self peptide is a nonallelically restricted immunomodulating peptide.

In further embodiments, the invention includes a method of identifying a potential immunomodulating peptide, in a method including the steps of:

(a) providing a cell expressing MHC class II molecules on its surface;

(b) introducing into the cell a nucleic acid encoding a candidate peptide; and

(c) determining whether the proportion of class II molecules which are bound to the candidate peptide is increased in the presence of the nucleic acid compared to the proportion bound in the absence of the nucleic acid, such an increase being an indication that the candidate peptide is a potential immunomodulating peptide.

Also within the invention is a method of identifying a potential immunomodulating peptide, which method includes the steps of:

(a) providing a cell expressing MHC class II molecules on its surface;

(b) introducing into the cell a nucleic acid encoding a candidate peptide; and

(c) determining whether the level of MHC class II molecules on the surface of the cell is decreased in the presence of the nucleic acid compared to the level of MHC class II molecules in the absence of the nucleic acid, such a decrease being an indication that the candidate peptide is a potential immunomodulating peptide.

Also included in the invention is a method of identifying a nonallelically restricted immunostimulating peptide, which method includes the steps of:

(a) providing a cell bearing a first MHC class I or class II allotype, such cell being infected with a pathogen (e.g., an infective agent which causes human or animal disease, such as human immunodeficiency virus (HIV), hepatitis B virus, measles virus, rubella virus, influenza virus, rabies virus, *Corynebacterium diphtheriae*, *Bordetella pertussis*, *Plasmodium spp.*, *Schistosoma spp.*, *Leishmania spp.*, *Trypanasoma spp.*, or *Mycobacterium lepre*);

(b) eluting a mixture of peptides bound to the cell's first MHC allotype;

(c) identifying a candidate peptide from the mixture, such candidate peptide being a fragment of a protein from the pathogen; and

(d) testing whether the candidate peptide binds to a second MHC allotype, such binding being an indication that the candidate peptide is a nonallelically restricted immunostimulating peptide. A nucleic acid encoding such an immunogenic fragment of a protein of a pathogen can be used in a method of inducing an immune response in a human patient, which method involves introducing the nucleic acid into an APC of the patient.

The therapeutic methods of the invention solve certain problems associated with prior art methods involving intravenous injection of synthetic peptides: (1) because of allelic specificity, a peptide capable of binding with high affinity to all, or even most, of the different class II allotypes expressed within the general population had not previously been identified; (2) the half-lives of peptides delivered intravenously are generally very low, necessitating repeated administration

with the associated high level of inconvenience and cost; (3) this type of delivery approach requires that the blocking peptide displace the naturally-occurring peptide occupying the binding cleft of a class II molecule while the latter is on the cell surface, which is now believed to be a very inefficient process; and (4) if the blocking peptide utilized is itself immunogenic, it may promote deleterious immune responses in some patients.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Detailed Description

The drawings are first briefly described.

Drawings

Figs. 1A-1F are chromatographic analyses of the peptide pools extracted from papain digested HLA-DR1, DR2, DR3, DR4, DR7, and DR8, respectively, illustrating the peptide repertoire of each HLA-DR as detected by UV absorbance. The UV absorbance for both 210 nm and 277 nm is shown at a full scale absorbance of 500 mAU with a retention window between 16 minutes and 90 minutes (each mark represents 2 minutes).

Fig. 2 is a representative mass spectrometric analysis of the size distribution of isolated HLA-DR1 bound peptides. The determined peptide masses in groups of 100 mass units were plotted against the number of isolated peptides identified by mass spectrometry. Peptide length was calculated by dividing the experimental mass by an average amino acid mass of 118 daltons.

Fig. 3A is a representation of a minigene of the invention (SEQ ID NO: 147), in which the HLA-DRα chain leader peptide is linked to the amino terminus of a 15-residue blocking peptide fragment of human invariant chain Ii.

Fig. 3B is a representation of a second minigene of the invention (SEQ ID NO: 148), in which the HLA-DRα chain leader peptide is linked to the amino terminus of a 24-residue blocking peptide fragment of human invariant chain Ii.

Experimental Data

METHODS

I. Purification of HLA-DR antigens.

HLA-DR molecules were purified from homozygous, Epstein-Barr virus-transformed, human B lymphoblastoid lines: DR1 from LG-2 cells, DR2 from MST cells, DR3 from WT20 cells, DR4 from Priess cells, DR7 from Mann cells, and DR8 from 23.1 cells. All of these cell lines are publicly available. Cell growth, harvest conditions and protein purification were as previously described (Gorga, J. et al., 1991). Briefly, 200 grams of each cell type was resuspended in 10mM Tris-HCl, 1mM dithiothreitol (DTT), 0.1mM phenylmethylsulfonylflouride (PMSF), pH 8.0, and lysed in a Thomas homogenizer. The nuclei were removed by centrifugation at 4000xg for 5 min and the pellets washed and repelleted until the supernatants were clear. All the supernatants were pooled and the membrane fraction harvested by centrifugation at 175,000xg for 40 min. The pellets were then resuspended in 10 mM Tris-HCl, 1mM DTT, 1mM PMSF, 4% NP-40. The unsolubilized membrane material was removed by centrifugation at 175,000xg for 2 hours, and the NP-40 soluble supernatant fraction used in immunoaffinity purification.

Detergent soluble HLA-DR was bound to a LB3.1-protein A sepharose column (Gorga et al., id) and eluted with 100 mM glycine, pH 11.5. Following elution, the sample was immediately neutralized by the addition of Tris-HCl and then dialyzed against 10mM Tris-HCl, 0.1% deoxycholic acid (DOC). The LB3.1 monoclonal antibody recognizes a conformational determinant present on the nonpolymorphic HLA-DRα chain, and thus recognizes all allotypes of HLA-DR.

The transmembrane domain of the DR molecules was removed by papain digestion, and the resulting water-soluble molecule further purified by gel filtration chromatography on an S-200 column equilibrated in 10mM Tris-HCl, pH 8.0. The purified DR samples were concentrated by ultrafiltration, yield determined by BCA assay, and analyzed by SDS polyacrylamide gel electrophoresis.

II. Extraction and fractionation of bound peptides.

Water-soluble, immunoaffinity-purified class II molecules were further purified by high-performance size exclusion chromatography (SEC), in 25 mM N-morpholino ethane sulfonic acid (MES) pH 6.5 and a flowrate of 1 ml/min., to remove any residual small molecular weight contaminants. Next, Centricon microconcentrators (molecular weight cutoff 10,000 daltons) (Amicon Corp.) were sequentially washed using SEC buffer and 10% acetic acid prior to spin-concentration of the protein sample (final volume between 100-200 μl). Peptide pools were extracted from chosen class II alleles by the addition of 1 ml of 10% acetic acid for 15 minutes at 70°C. These conditions are sufficient to free bound peptide from class II molecules, yet mild enough to avoid peptide degradation. The peptide pool was separated from the class II molecule after centrifugation through the

Centricon concentrator, with the flow-through containing the previously bound peptides.

The collected acid-extracted peptide pool was concentrated in a Savant Speed-Vac to a volume of 50 µl prior to HPLC separation. Peptides were separated on a microbore C-18 reversed-phase chromatography (RPC) column (Vydac) utilizing the following non-linear gradient protocol at a constant flowrate of 0.15 ml/min.: 0-63 min. 5%-33% buffer B; 63-95 min. 33%-60% buffer B; 95-105 min 60%-80% buffer B, where buffer A was 0.06% trifluoroacetic acid/water and buffer B was 0.055% trifluoroacetic acid/acetonitrile. Chromatographic analysis was monitored at multiple UV wavelengths (210, 254, 277, and 292 nm) simultaneously, permitting spectrophotometric evaluation prior to mass and sequence analyses. Shown in Fig.1 are chromatograms for each of the six DR peptide pools analyzed. Collected fractions were subsequently analyzed by mass spectrometry and Edman sequencing.

III. Analysis of peptides.

The spectrophotometric evaluation of the peptides during RPC provides valuable information regarding amino acid composition (contribution of aromatic amino acids) and is used as a screening method for subsequent characterization. Appropriate fractions collected during the RPC separation were next analyzed using a Finnegan-MAT LaserMat matrix-assisted laser-desorption mass spectrometer (MALD-MS) to determine the individual mass values for the predominant peptides. Between 1%-4% of the collected fraction was mixed with matrix (1µl α-Cyano-4-hydroxycinnamic acid) to achieve mass determination of extracted peptides. The result of this analysis for HLA-DR1 is shown in Fig. 2. Next, chosen peptide samples were sequenced by automated Edman

degradation microsequencing using an ABI 477A protein sequencer (Applied Biosystems) with carboxy-terminal verification provided by mass spectral analysis using the Finnigan-MAT TSQ 700 triple quadruple mass spectrometer equipped with an electro-spray ion source. This parallel analysis ensures complete identity of peptide composition and sequence. Peptide alignment with protein sequences stored in the SWISS-PROT database was performed using the FASTA computer database search program. Set forth in Tables 1-10 are the results of this sequence analysis for each of the DR molecules studied.

RESULTS

I. HLA-DR1.

The HLA-DR1 used in this study was papain solubilized to enable the material to be used both for crystallographic and bound peptide analyses. The peptides bound to DR1 were acid extracted and fractionated using RPC (Fig. 1). The absence of any detectable peptidic material following a second extraction/RPC separation verified quantitative peptide extraction. Amino acid analysis (ABI 420A/130A derivatizer/HPLC) of extracted peptide pools demonstrated a 70-80% yield, assuming total occupancy of purified DR1 with a molar equivalent of bound peptides corresponding to the size distribution determined by mass spectrometry (see Fig. 2). The RPC profiles obtained from DR1 extractions of multiple independent preparations were reproducible. Furthermore, profiles from either detergent-soluble or papain-solubilized DR1 were equivalent. To confirm that the peptides were in fact identical in detergent-soluble and papain-digested DR1, mass spectrometry and Edman sequencing analyses were performed and revealed identical masses and sequences for analogous fractions from the two preparations.

Matrix-assisted laser desorption mass spectrometry (MALD-MS) was used to identify 111 species of unique mass contained within the eluted peptide pool of DR1 with an average size of 18 and a mode of 15 residues (Fig. 2). Over 500 additional mass species present within the molecular weight range of 13-25 residues were detected; however, the signal was not sufficient to assign individual masses with confidence. Multiple species of varying mass were detected in fractions corresponding to single RPC peaks indicating co-elution of peptides. To characterize these peptides further, samples were analyzed in parallel on a triple quadruple mass spectrometer equipped with an electrospray ion source (ESI-MS) and by automated Edman degradation microsequencing (Lane et al., J. Prot. Chem. 10:151-160 (1991)). Combining these two techniques permits crucial verification of both the N- and C-terminal amino acids of peptides contained in single fractions. The sequence and mass data acquired for twenty peptides isolated from DR1 are listed in Table 1. All the identified peptides aligned with complete identity to regions of proteins stored in the SWISS-PROT database.

Surprisingly, sixteen of the twenty sequenced DR1-bound peptides were 100% identical to regions of the self proteins HLA-A2 and class II-associated invariant chain (Ii), representing at least 26% of the total extracted peptide mass. These isolated peptides varied in length and were truncated at both the N- and C-termini, suggesting that: 1) antigen processing occurs from both ends after binding to DR1, or 2) class II molecules bind antigen from a pool of randomly generated peptides. The yields from the peptide microsequencing indicated that HLA-A2 (Fig. 1) and Ii each represents at least 13% of the total DR1-bound peptides.

An additional surprising finding concerned a peptide which, although bound to HLA-DR and 100% homologous with

HLA-A2 peptide, was derived from a cell which does not express HLA-A2 protein. Evidently this peptide is derived from a protein containing a region homologous with a region of HLA-A2 protein. Thus, for purposes of this specification, the term "HLA-A2 protein" is intended to include HLA-A2 protein itself, as well as any naturally occurring protein which contains a ten or greater amino acid long region of >80% homology with an HLA-DR-binding peptide derived from HLA-A2. An "HLA-A2 peptide" similarly refers to peptides from any HLA-A2 protein, as broadly defined herein.

The other four peptides identified in the DR1 studies were derived from two self proteins, transferrin receptor and the Na^+/K^+ ATPase, and one exogenous protein, bovine serum fetuin (a protein present in the serum used to fortify the medium which bathes the cells). Each of these peptides occupied only 0.3-0.6% of the total DR1 population, significantly less than either the HLA-A2 or the Ii peptides. It is known that class II molecules en route to the cell surface intersect the pathway of incoming endocytic vesicles. Both recycling membrane proteins and endocytosed exogenous protein travel this common pathway. Hence, the HLA-A2, transferrin receptor, Na^+/K^+ ATPase and bovine fetuin derived peptides would all encounter DR1 in a similar manner. Ii associates with nascent class II molecules in the endoplasmic reticulum (ER) (Jones et al., Mol. Immunol. 16:51-60 (1978)), preventing antigen binding until the class II/Ii complex arrives at an endocytic compartment (Roche and Cresswell, Nature 345:615-618 (1990)), where Ii undergoes proteolysis (Thomas et al., J. Immunol. 140:2670-2675 (1988); Roche and Cresswell, Proc. Natl. Acad. Sci. USA 88:3150-3154 (1991)), thus allowing peptide binding to proceed. Presumably, the Ii peptides bound to DR1 were generated at this step.

Synthetic peptides corresponding to five of the peptides reported in Table 1 were made and their relative binding affinities to DR1 determined. The influenza A hemagglutinin peptide (HA) 307-319 (SEQ ID NO: 24) has been previously described as a high affinity, HLA-DR1 restricted peptide (Roche and Cresswell, J. Immunol. 144:1849-1856 (1990); Rothbard et al., Cell 52:515-523 (1988)), and was thus chosen as the control peptide. "Empty" DR1 purified from insect cells expressing recombinant DR1 cDNA was used in the binding experiments because of its higher binding capacity and 10-fold faster association kinetics than DR1 isolated from human cells (Stern and Wiley, Cell 68:465-477 (1992)). All the synthetic peptides were found to compete well (Ki < 100 nM) against the HA peptide (Table 2). At first approximation, the Ii 106-119 peptide (SEQ ID NO: 156) had the highest affinity of all the competitor peptides measured, equivalent to that determined for the control HA peptide. In addition to the Ki determinations, these peptides were found to confer resistance to SDS-induced α-β chain dissociation of "empty" DR1 when analyzed by SDS-PAGE, indicative of stable peptide binding (Sadegh-Nasseri and Germain, Nature 353:167-170 (1991); Dornmair et al., Cold Spring Harbor Symp. Quant. Biol. 54:409-415 (1989); Springer et al., J. Biol. Chem. 252:6201-6207 (1977)). Neither of the two control peptides, β_2m 52-64 (SEQ ID NO: 26) nor Ii 96-110 (SEQ ID NO: 25), was able to either confer resistance to SDS-induced chain dissociation of DR1 or compete with HA 307-319 (SEQ ID NO: 24) for binding to DR1; both of these peptides lack the putative binding motif reported in this study (see below).

A putative DR1 binding motif based on the sequence alignments of the core epitopes (the minimum length) of certain naturally processed peptides is shown in Table 3. The peptides listed in this table include those determined

herein for HLA-DR1, as well as a number of peptides identified by others and known to bind DR1 (reference #6 in this table being O'Sullivan et al., J. Immunol. 145:1799-1808, 1990; reference #17, Roche & Cresswell, J. Immunol. 144:1849-1856, 1990; reference #25, Guttinger et al., Intern. Immunol. 3:899-906, 1991; reference #27, Guttinger et al. EMBO J. 7:2555-2558, 1988; and reference #28, Harris et al., J. Immunol. 148:2169-2174, 1992). The key residues proposed in the motif are as follows: a positively charged group is located at the first position, referred to here as the index position for orientation (I); a hydrogen bond donor is located at I+5; and a hydrophobic residue is at I+9. In addition, a hydrophobic residue is often found at I+1 and/or I-1. Every naturally processed peptide sequenced from DR1 conforms to this motif (with the exception of the HLA-A2 peptide 103-116 (SEQ ID NO: 3) that lacks residue I+9). Because the putative motif is not placed in a defined position with respect to the first amino acid and because of the irregular length of bound peptides, it is impossible to deduce a motif from sequencing of peptide pools, as was done for class I molecules (Falk et al., Nature 351:290-296 (1991)). The Ii 96-110 peptide (SEQ ID NO: 25), a negative control peptide used in binding experiments, has the I and I+5 motif residues within its sequence, but is missing eight additional amino acids found in Ii 105-118 (SEQ ID NO: 16) (Table 3C).

A sequence comparison of 35 previously described DR1-binding synthetic peptides (O'Sullivan et al., J. Immunol. 145:1799-1808 (1990); Guttinger et al., Intern. Immunol. 3:899-906 (1991); Hill et al., J. Immunol. 147:189-197 (1991); Guttinger et al., EMBO J. 7:2555-2558 (1988); Harris et al., J. Immunol. 148:2169-2174 (1992)) also supports this motif. Of the 35 synthetic peptides, 21 (60%) have the precise motif, nine (30%) contain a single

shift at either I or I+9, and the remaining five (10%) have a single substitution at I (Table 3B and C). Interestingly, in the latter peptides, a positive charge at I is always replaced by a large hydrophobic residue (Table 8C); a pocket has been described in class I molecules that can accommodate this precise substitution (Latron et al., Proc. Natl. Acad. Sci. USA 88:11325-11329 (1991)). Contributions by the other eight amino acids within the motif or the length of the peptide have not been fully evaluated and may compensate for shifted/missing residues in those peptides exhibiting binding. Evaluation of the remaining 117 non-DR1 binding peptides cited in those studies (which peptides are not included in Table 3) indicates that 99 (85%) of these peptides do not contain the DR1 motif proposed herein. Of the remaining 18 peptides (15%) that do not bind to DR1 but which do contain the motif, 6 (5%) are known to bind to other DR allotypes; the remaining 12 peptides may have unfavorable interactions at other positions which interfere with binding.

In contrast to the precise N-terminal cleavages observed in the previous study of six peptides bound to the mouse class II antigen termed I-A^b and five bound to mouse I-E^b (Rudensky et al., Nature 3563:622-627 (1991)), the peptides bound to DR1 are heterogeneous at both the N- and C-termini. In contrast to peptides bound to class I molecules, which are predominantly nonamers (Van Bleek and Nathenson, Nature 348:213-216 (1990); Rotzschke et al., Nature 348:252-254 (1990); Jardetzky et al., Nature 353:326-329 (1991); Hunt et al., Science 255:1261-1263 (1992)), class II peptides are larger and display a high degree of heterogeneity both in length and the site of terminal truncation, implying that the mechanisms of processing for class I and class II peptides are substantially different. Furthermore, the present results suggest that class II processing is a stochastic event and

that a DR allotype may bind peptides of different lengths from a complex random mixture. The heterogeneity observed may be solely due to protection of bound peptides from further degradation. Thus, class II molecules would play an active role in antigen processing (as previously proposed (Donermeyer and Allen, J. Immunol. 142:1063-1068 (1989)) by protecting the bound peptides from complete degradation. Alternatively, the predominance of 15mers bound to DR1 (as detected by both the MALD-MS and the yields of sequenced peptides) could be the result of trimming of bound peptides. In any event, the absence of detectable amounts of peptides shorter than 13 and longer than 25 residues suggests that there are length constraints intrinsic either to the mechanism of peptide binding or to antigen processing. The predominance of peptides bound to DR1 that are derived from endogenously synthesized proteins, and particularly MHC-related proteins, may result from the evolution of a mechanism for presentation of self peptides in connection with the generation of self tolerance.

II. Other HLA-DR molecules.

The sequences of naturally processed peptides eluted from each of DR2, DR3, DR4, DR7 and DR8 are shown in Tables 4-8, respectively. In addition to those peptides shown in Table 4, it has been found that DR2 binds to long fragments of HLA-DR2a β-chain and HLA-DR2b β-chain, corresponding to residues 1-126 or 127 of each of those proteins. Presumably, only a short segment of those long fragments is actually bound within the groove of DR2, with the remainder of each fragment protruding from one or both ends of the groove. Table 9 gives sequences of DR1 from another cell line which does not have wild-type Ar, but which has bound A2-like peptides. Table 10 gives sequences of peptides eluted from DR4 and DR11 molecules expressed in

cells from a human spleen. These data demonstrate the great prevalence of self peptides bound, compared to exogenous peptides. The data also show that the A2 and Ii peptides occur repeatedly. In addition, certain of the Tables include peptides that appear to derive from viral proteins, such as Epstein-Barr virus major capsid protein, which are likely to be present in the cells studied.

III. Peptide Delivery

Genetic Constructions.

In order to prepare genetic constructs for in vivo administration of genes encoding immunomodulatory peptides of the invention, the following procedure is carried out.

Overlapping synthetic oligonucleotides were used to generate the leader peptide/blocking peptide mini-genes illustrated in Fig. 3 by PCR amplification from human HLA-DRα and invariant chain cDNA templates. These mini-genes encode the Ii peptide fragments KMRMATPLLMQALPM (or Ii_{15}; SEQ ID NO: 15) and LPKPPKPVSKMRMATPLLMQALPM (or Ii_{24}; SEQ ID NO: 7). The resulting constructs were cloned into pGEM-2 (Promega Corp.) to form the plasmids pGEM-2-α-Ii_{15} and pGEM-2-α-Ii_{24}, with an upstream T7 promoter for use in the in vitro transcription/translation system described below.

For in vivo expression, each mini-gene was subsequently subcloned from the pGEM-2 derivatives into a transfection vector, pHβactin-1-neo (Gunning et al., (1987) Proc. Natl. Acad. Sci. U.S.A. 84:4831), to form the plasmids pHβactin-α-Ii_{15} and pHβactin-α-Ii_{24}. The inserted mini-genes are thus expressed in vivo from the constitutive/strong human β actin promoter. In addition, the mini-genes were subcloned from the pGEM-2 derivatives into the vaccinia virus recombination vector pSC11 (S. Chakrabarti et al. (1985) Mol. Cell. Biol. 5, 3403-3409) to form the plasmids pSC11-α-Ii_{15} and pSC11-α-Ii_{24}. Following

recombination into the viral genome the inserted mini-genes are expressed from the strong vaccinia $p_{7.5}$ promoter.

Intracellular trafficking signals added to peptides.

Short amino acid sequences can act as signals to target proteins to specific intracellular compartments. For example, hydrophobic signal peptides are found at the amino terminus of proteins destined for the ER, while the sequence KFERQ (SEQ ID NO: 153) (and other closely related sequences) is known to target intracellular polypeptides to lysosomes, while other sequences target polypeptides to endosomes. In addition, the peptide sequence KDEL (SEQ ID NO: 152) has been shown to act as a retention signal for the ER. Each of these signal peptides, or a combination thereof, can be used to traffic the immunomodulating peptides of the invention as desired. For example, a construct encoding a given immunomodulating peptide linked to an ER-targeting signal peptide would direct the peptide to the ER, where it would bind to the class II molecule as it is assembled, preventing the binding of intact Ii which is essential for trafficking. Alternatively, a construct can be made in which an ER retention signal on the peptide would help prevent the class II molecule from ever leaving the ER. If instead a peptide of the invention is targeted to the endosomic compartment, this would ensure that large quantities of the peptide are present when invariant chain is replaced by processed peptides, thereby increasing the likelihood that the peptide incorporated into the class II complex is the high-affinity peptides of the invention rather than naturally-occurring, potentially immunogenic peptides. The likelihood of peptides of the invention being available incorporation into class II can be increased by linking the peptides to an intact Ii polypeptide sequence. Since Ii is known to traffic class II molecules to the endosomes, the hybrid Ii would

carry one or more copies of the peptide of the invention along with the class II molecule; once in the endosome, the hybrid Ii would be degraded by normal endosomal processes to yield both multiple copies of the peptide of the invention or molecules similar to it, and an open class II binding cleft. DNAs encoding immunomodulatory peptides containing targeting signals will be generated by PCR or other standard genetic engineering or synthetic techniques, and the ability of these peptides to associate with DR molecules will be analyzed in vitro and in vivo, as described below.

It is proposed that the invariant chain prevents class II molecules from binding peptides in the ER and may contribute to heterodimer formation. Any mechanism that prevents this association would increase the effectiveness of class II blockade. Therefore, a peptide corresponding to the site on Ii which binds to the class II heterodimer, or corresponding to the site on either the α or β subunit of the heterodimer which binds to Ii, could be used to prevent this association and thereby disrupt MHC class II function.

In Vitro Assembly.

Cell free extracts are used routinely for expressing eukaryotic proteins (Krieg, P. & Melton, D. (1984) Nucl. Acids Res. 12, 7057; Pelham, H. and Jackson, R. (1976) Eur. J. Biochem. 67, 247). Specific mRNAs are transcribed from DNA vectors containing viral RNA polymerase promoters (Melton, D. et al. (1984) Nucl. Acids Res. 12, 7035), and added to micrococcal nuclease-treated cell extracts. The addition of ^{35}S methionine and amino acids initiates translation of the exogenous mRNA, resulting in labeled protein. Proteins may be subsequently analyzed by SDS-PAGE and detected by autoradiography. Processing events such as signal peptide cleavage and core glycosylation are

initiated by the addition of microsomal vesicles during translation (Walter, P. and Blobel, G. (1983), Meth. Enzymol., 96, 50), and these events are monitored by the altered mobility of the proteins in SDS-PAGE gels.

The ability of peptides containing a signal peptide sequence to be accurately processed and to compete with invariant chain for class II binding in the ER are assayed in the in vitro system described above. Specifically, DR1 α- and β-chain and invariant chain peptide constructs described above are transcribed into mRNAs, which will be translated in the presence of mammalian microsomal membranes. Association of the DR heterodimer with Ii is determined by immunoprecipitation with antisera to DR and Ii. Addition of mRNA encoding the peptide of the invention to the translation reaction should result in a decreased level of coimmunoprecipitated Ii, and the concomitant appearance of coimmunoprecipitated peptide, as determined by SDS-PAGE on TRIS-Tricine gels. These experiments will provide a rapid assay system for determining the potential usefulness of a given blocking peptide as a competitor for Ii chain binding in the ER. Those peptides of the invention which prove to be capable of competing successfully with Ii in this cell-free assay can then be tested in intact cells, as described below.

In Vivo Assembly.

Human EBV-transformed B cell lines LG-2 and HOM-2 (homozygous for HLA-DR1) and the mouse B cell hybridoma LK35.2 are transfected with either 50μg of linearized pHβactin-α-Ii_{15} or pHβactin-α-Ii_{24} or (as a control) pHβactin-1-neo by electroporation (150mV, 960μF, 0.2cm cuvette gap). Following electroporation, the cells are cultured in G418-free medium until total recovery (approximately 4 days). Each population is then placed under G418 selection until neomycin-expressing resistant

populations of transfectants are obtained (approximately 1-2 months). The resistant populations are subcloned by limiting dilution and the clonality of stable transfectants determined by PCR amplification of blocking peptide mRNA expression.

Stable transfectants of LG-2 and HOM-2 carrying blocking peptide mini-genes or negative control vectors are grown in large-scale culture conditions until 20 grams of pelleted cell mass is obtained. The HLA-DR expressed by each transfectant is purified, and the bound peptide repertoire (both from within the cell and from the cell surface) analyzed as described above. Successful demonstration of a reduction in the total bound peptide diversity will be conclusive evidence of intracellular delivery of immuno-modulatory peptides.

A second cell-based assay utilizes stable transfectants of LK35.2 cells carrying blocking peptide mini-genes or negative control vectors; these cells are used as APCs in T cell proliferation assays. Each transfectant is cultured for 24 hours in the presence of different dilutions of hen egg lysozyme (HEL) and HEL-specific T cell hybridomas. The relative activation of the T cells present in each assay (as measured by lymphokine production) is determined using the publicly available lymphokine dependent cell line CTLL2 in a ^{3}H-thymidine incorporation assay (Vignali et al. (1992) J.E.M. 175:925-932). Successful demonstration of a reduction in the ability of blocking peptide expressing transfectants to present HEL to specific T cell hybridomas will be conclusive evidence of intracellular delivery of immuno-modulatory peptides. Cells of the human TK^- cell line 143 (ATCC) are infected with vaccinia virus (strain WR, TK^+) (ATCC), and two hours postinfection, pSC11-α-Ii_{15} or pSC11-α-Ii_{24} or pSC11 is introduced into the infected cells by calcium phosphate precipitation. TK^- recombinants are

selected for with bromodeoxyuridine at 25μg/ml. Recombinant plaques are screened by PCR for the presence of mini-gene DNA. Recombinant virus is cloned by three rounds of limiting dilution to generate pure clonal viral stocks.

In experiments analogous to the transfection experiments described above, recombinant vaccinia viruses encoding mini-genes or vector alone will be used to infect large-scale cultures of the human EBV transformed B cell lines LG-2 and HOM-2. Following infection, the HLA-DR is purified and the bound peptide repertoire analyzed as described above. A reduction of the complexity of the bound peptide population and a significant increase in the relative amount of Ii peptides bound are conclusive evidence that vaccinia can deliver blocking peptides to human APCs.

The same recombinant vaccinia viruses encoding mini-genes or vector will be used to infect mice experiencing experimentally-induced autoimmunity. A number of such models are known and are referred in Kronenberg, Cell 65:537-542 (1991).

Liposomal Delivery of Synthetic Peptides or Mini-gene Constructs.

Liposomes have been successfully used as drug carriers and more recently in safe and potent adjuvant strategies for malaria vaccination in humans (Fries et al. (1992), Proc. Natl. Acad. Sci. USA 89:358). Encapsulated liposomes have been shown to incorporate soluble proteins and deliver these antigens to cells for both in vitro and in vivo $CD8^+$ mediated CTL response (Reddy et al., J. Immunol. 148:1585-1589, 1992; and Collins et al., J. Immunol. 148:3336-3341, 1992). Thus, liposomes may be used as a vehicle for delivering synthetic peptides into APCs.

Harding et al. (Cell (1991) 64, 393-401) have demonstrated that the targeting of liposome-delivered

antigen to either of two intracellular class II-loading compartments, early endosomes and/or lysosomes, can be accomplished by varying the membrane composition of the liposome: acid-sensitive liposomes were found to target their contents to early endosomes, while acid-resistant liposomes were found to deliver their contents to lysosomes. Thus, the peptides of the invention will be incorporated into acid-sensitive liposomes where delivery to endosomes is desired, and into acid-resistant liposomes for delivery to lysosomes.

Liposomes are prepared by standard detergent dialysis or dehydration-rehydration methods. For acid-sensitive liposomes, dioleoylphosphatidylethanolamine (DOPE) and palmitoylhomocystein (PHC) are utilized, while dioleoylphospatidylcholine (DOPC) and dioleoylphosphatidylserine (DOPS) are used for the preparation of acid-resistant liposomes. 10^{-5} mol of total lipid (DOPC/DOPS or DOPE/PHC at 4:1 mol ratios) are dried, hydrated in 0.2 ml of HEPES buffered saline (HBS) (150 mM NaCl, 1 mM EGTA, 10mM HEPES pH 7.4) and sonicated. The lipid suspensions are solubilized by the addition of 0.1 ml of 1 M octylglucoside in HBS. The peptides to be entrapped are added to 0.2 ml of 0.6 mM peptide in 20% HBS. The mixture is then frozen, lyophilized overnight, and rehydrated. These liposomes will be treated with chymotrypsin to digest any surface-bound peptide. Liposome delivery to EBV-transformed cell lines (as described above) will be accomplished by 12-16 hour incubation at 37°C. HLA-DR will be purified from the liposome treated cells and bound peptide analyzed as above.

Alternatively, the liposomes are formulated with the DNA mini-gene constructs of the invention, and used to deliver the constructs into APCs either <u>in vitro</u> or <u>in vivo</u>.

Human immunization will be carried out under the protocol approved by both The Johns Hopkins University Joint Committee for Clinical Investigation and the Human Subject Research Review Board of the Office of the Surgeon General of the U.S. Army (Fries et al. (1992), Proc. Natl. Acad. Sci. U.S.A. 89:358-362), using dosages described therein, or other dosages described in the literature for liposome-based delivery of therapeutic agents.

Delivery via Immune-stimulating Complexes (ISCOMS).

ISCOMS are negatively charged cage-like structures of 30-40nm in size formed spontaneously on mixing cholesterol and Quil A (saponin). Protective immunity has been generated in a variety of experimental models of infection, including toxoplasmosis and Epstein-Barr virus-induced tumors, using ISCOMS as the delivery vehicle for antigens (Mowat and Donachie) Immunology Today 12:383-385, 1991. Doses of antigen as low as 1μg encapsulated in ISCOMS have been found to produce class I mediated CTL responses, where either purified intact HIV-1-IIIB gp 160 envelope glycoprotein or influenza hemagglutinin is the antigen (Takahashi et al., Nature 344:873-875, 1990). Peptides are delivered into tissue culture cells using ISCOMS in a manner and dosage similar to that described above for liposomes; the class II peptide binding of delivered peptides are then determined by extraction and characterization as described above. ISCOM-delivered peptides of the invention which are effectively utilized by cultured cells are then tested in animals or humans.

In addition to delivery of the therapeutic synthetic peptides, ISCOMS could be constituted to deliver the mini-gene constructs to APCs, and thus serve as an alternative to the above-outlined vaccinia strategy.

Immunogenic Peptide Delivery (Vaccines).

In addition to using the above-described intracellular delivery systems to deliver nonimmunogenic self peptides with the specific aim of down-modulating the immune system (thus alleviating autoimmune conditions), the delivery systems of the invention may alternatively be used as a novel means of vaccination, in order to stimulate a portion of the immune system of an animal. In the latter context, the delivery system is employed to deliver, into appropriate cells, DNA constructs which express immunogenic, pathogen-derived peptides intended to stimulate an immune response against a specific pathogen. Because the antigenic peptide is produced inside the target cell itself, the vaccine method of the invention ensures that there is no circulating free antigen available to stimulate antibody formation and thereby induce potentially deleterious or inappropriate immunological reactions. The immune response stimulated by vaccines of the invention is, because the vaccines are targeted solely to APC's, limited to the T cell mediated response, in contrast to standard vaccine protocols which result in a more generalized immune response. Although some of the peptide-presenting APC's will initially be lysed by host T cells, such lysis will be limited because, inter alia, the virus-based vaccine is non-replicative, i.e., each carrier virus can infect only one cell.

The model antigen that will be used to perfect and test the system of the invention is hen egg lysozyme (HEL). It is arguably the most well characterized protein for antigen presentation studies, to which there are numerous monoclonal antibodies and class I- and class II-restricted mouse T cell clones and hybridomas. The primary epitopes that will be studied are the peptide HEL 34-45, as both monoclonal antibodies and CD4+ T cell hybridomas are available, and peptide HEL 46-61, as both class I and class

II-restricted T cell clones and hybridomas have been raised and are publicly available. These two sequences are thus proven immunogenic epitopes. Initially, four constructs encoding different polypeptides are analyzed: (a) whole, secreted HEL, (B) HEL 34-45, (c) HEL 46-61, and (d) HEL 34-61. The last three include a signal sequence known to be cleaved in these cells, e.g., IA^k (MPRSRALILGVLALTTMLSLCGG; SEQ ID NO:), which would result in targeting to the ER. All constructs are then subcloned into pHβApr-1 neo. The methodology for making these constructs is similar to that outlined above. The constructs are introduced into appropriate APCs, e.g., LK35.2 cells, by means of a conventional eukaryotic transfection or one of the delivery vehicles discussed above (e.g., vaccinia, liposomes, or ISCOMS). LK35.2 cells, which possess the mouse MHC Class II restriction molecules IA^k and IE^k, transfected with each of the constructs are tested for their ability to stimulate the appropriate class I and class II-restricted T cell hybridomas and clones using standard techniques. Whether class I stimulation is observed will depend on whether peptide trimming can occur in the ER, in order to produce an 8-10-mer suitable for binding to class I molecules. If these constructs are ineffective for class I stimulation, they can be modified in order to produce a more effective peptide for class I binding. If these constructs prove to be less effective for class II-restricted responses, they can be tagged with endosomal and/or lysosomal targeting sequences as discussed in Section V.

The effectiveness of targeting signals used to direct immunogenic peptides to particular intracellular organelles would be monitored using electron microscopic analysis of immunogold stained sections of the various transfectants. Rabbit anti-peptide antisera would be produced and affinity purified for this application. In

addition, monoclonal antibody HF10, which recognizes HEL 34-45, will be used.

Once a construct is defined that can be effectively presented by transfectants in vitro, its effectiveness in vivo will be determined. This can be tested by injection of the transfectants i.p. and/or s.c. into C3H/Balb/c F1 mice, or by injection of the construct incorporated into an appropriate delivery vehicle (e.g., liposome, ISCOMS, retrovirus, vaccinia). Optimal protocols and doses for such immunizing injections can be determined by one of ordinary skill in the art, given the disclosures provided herein. Efficiency of immunization can be tested by standard methods such as (a) proliferation of class II-restricted T cells in response to HEL pulsed APCs, (b) CTL response to ^{51}Cr-labeled targets, and (c) serum antibody titre as determined by ELISA.

Once the details of the vaccine delivery system of the invention are optimized, constructs encoding peptides with useful immunizing potential can be incorporated into the system. Such peptides can be identified by standard means now used to identify immunogenic epitopes on pathogen-derived proteins. For example, candidate peptides for immunization may be determined from antibody and T cell analysis of animals infected with a particular pathogen. In order to obtain a protective and effective anamnestic response, the peptides used for vaccination should ideally be those which are presented with the highest frequency and efficiency upon infection. This could best be determined by using the procedures outlined in the experimental section above to extract and characterize the peptides bound by MHC class II molecules from infected cells. Given allelic restriction of immunogenic peptides (in contrast to the observed degenerate binding of self peptides of invention), a mini-gene encoding several immunogenic peptides will probably be required to provide a vaccine

useful for the entire population. Vaccine administration and dosage are as currently employed to smallpox vaccination.

TABLE 1

LG-2/HLA-DR1 BINDING PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC	YIELD
Pseudo HLA-A2	103-120	VGSDWRFLRGYHQYAYDG	1	18	DR1S-59	2190.4	2190.4	39.5
	103-117	VGSDWRFLRGYHQYA	2	15	DR1S-58	1855.0	1854.4	907.5
	103-116	VGSDWRFLRGYHQY	3	14	DR1S-58	1784.0	1783.6	53.3
	104-117	GSDWRFLRGYHQYA	4	14	DR1S-56	1755.3	1755.2	96.5
	105-117	SDWRFLRGYHQYA	5	13	DR1S-56	1698.2	1698.8	48.8
Invariant Chain (Ii)	97-121	LPKPPKPVSKMRMATPLLMQALPMG	6	25	DR1S-88	2733.5	2734.5	40.5
	97-120	LPKPPKPVSKMRMATPLLMQALPM	7	24	DR1S-88	2676.4	2675.9	80.8
	98-121	PKPPKPVSKMRMATPLLMQALPMG	8	24	DR1S-86	2620.2	2619.7	91.5
	97-119	LPKPPKPVSKMRMATPLLMQALP	9	23	DR1S-86	2545.2	2544.5	112.2
	98-120	PKPPKPVSKMRMATPLLMQALPM	10	23	DR1S-87	2563.2	2562.3	145.0
	99-120	KPPKPVSKMRMATPLLMQALPM	11	22	DR1S-87	2466.1	2465.8	101.5
	98-119	PKPPKPVSKMRMATPLLMQALP	12	22	DR1S-84	2432.0	2431.7	72.5
	99-119	KPPKPVSKMRMATPLLMQALP	13	21	DR1S-84	2334.9	2334.2	31.6
	100-119	PPKPVSKMRMATPLLMQALP	14	20	DR1S-86	2206-7	2207.4	89.8
	106-120	KMRMATPLLMQALPM	15	15	DR1S-88	1732.2	1731.9	178.5
	106-119	KMRMATPLLMQALP	16	14	DR1S-86	1601.0	1600.2	162.0
Na+/K+ ATPase	199-216	IPADLRIISANGCKVDNS	17	18	DR1S-56	1886.6	1885.8	48.8
Transferrin Recpt.	680-696	RVEYHFLSPYVSPKESP	18	17	DR1S-58	2035.3	2036.8	30.3
Bovine Fetuin	56-74	YKHTLNQIDSVKVWPRRPT	19	19	DR1S-51	2237.6	2236.5	69.0
	56-73	YKHTLNQIDSVKVWPRRP	20	18	DR1S-50	2338.7	2338.5	32.5
HLA-DR β-chain	43-61	DVGEYRAVTELGRPDAEYW	21	19	DR1S-51	2226.5	?	
Carboxypeptidase E	101-115	EPGEPEFKYIGNMHG	22	15	DR1S-48	1704.9	1700.4* ESI-MS	

TABLE 2

PEPTIDE BINDING TO HLA-DR1

PEPTIDE[a]	SEQ ID NO.	LENGTH	Ki vs HA 307-319[b] nM	SDS-Resistance[c] TM
HLA-A2 103-117	2	15	49 ± 3	+
Ii 105-119	15	15	< 10	+
Ii 97-120	7	24	33 ± 5	+
Na+/K+ ATPase 199-216	17	18	68 ± 9	+
Transf. Recept. 680-696	18	17	< 10	+
Bovine Fetuin 56-72	23	19	66 ± 18	+
HA 307-319	24	14	< 10	+
Ii 97-111	25	15	> 10^4	-
β_2m 52-64	26	13	> 10^4	-

a The first six entries correspond to peptides found associated with HLA-DR1 and the sequences are shown in Table 1. Two control peptides were also tested: β_2m 52-64, SDLSFSKDWSFYL, is from human β_2-microglobulin and Ii 96-110, LPKPPKPVSKMRMAT is a truncated version of the longest invariant chain derived peptide isolated from HLA-DR1. Peptides were synthesized using solid-phase Fmoc chemistry, deprotected and cleaved using standrd methods, then purified by RPC. Purified peptides were analyzed by mass spectrometry and concentrations were determined by quantitative ninhydrin analysis.

b Inhibition constants (Ki) were measured as the concentration of test peptide which inhibited 50% of the ^{125}I-labeled HA 307-319 binding to "empty" HLA-DR1 produced in Sf9 insect cells (20). HA 307-319 was labeled using Na^{125}I and chloramine-T and isolated by gel filtration. Specific activity, determined by BCA assay (Pierce) and gamma counting, was 26,000 cpm/pmol. 10nM labeled peptide and 10 nM purified HLA-DR1 were mixed with 10 different concentrations (10 nM to 10 μM) of synthetic cold competitor peptide in phosphate-buffered saline, pH 7.2, containing 1 mM EDTA, 1mM PMSF, 0.1 mM iodoacetamide, and 3 mM NaN_3, and incubated at 37°C for 85 hours. Free and bound peptide were separated by native gel electrophoresis (33) and bound radioactivity was quantitated using a Fujix imaging plate analyzer (BAS 2000) after four hour exposures on the phospho-imaging plates. Percent inhibition was calculated as the ratio of background-corrected radioactivity in the sample to background-corrected radioactivity in a parallel sample containing no competitor peptide. Under these conditions, Ki measurements < 10 nM could not be accurately determined.

c The ability of the synthetic peptides to confer resistance to SDS-induced chain dissociation of HLA-DR1 produced in insect cells was determined as described (20). Briefly, 20 μM HLA-DR1 was incubated with five-fold excess of synthetic peptide at 37°C for 85 hours, in phosphate-buffered saline (pH 7.2) with the protease inhibitor mixture described above. After incubation, the samples were analyzed by SDS-PAGE with and without boiling prior to loading. Peptides which prevented SDS-induced chain dissociation are indicated positive (+) and those that did not negative (-).

TABLE 3 - PUTATIVE HLA-DR1 PEPTIDE BINDING MOTIF

	PROTEIN SOURCE	PEPTIDE SEQUENCE	SEQ ID NO.	LENGTH	POSITION	REFERENCE
A	HLA-A2	SDWRFLRGYHQYA	5	13	105-117	This study
	Invariant Chain	KMRMAIPLLMQALP	16	14	105-118	
	Na+/K+ ATPase	IPADLRIISANGCKVDNS	17	18	199-216	
	Transferrin Receptor	RVEYMFLSPIVSPKESP	18	17	680-696	
	Bovine Fetuin	YKMTLMQIDSVKVWPRRP	20	18	56-73	
B	HEL	KVFGRCELAAAMKRHGLD	27	18	1-18	6
		RHRCKGTDVQAWIRGCRL	28	18	112-129	6
	β_2^m	MPPHIEIQMLKNGKKI	29	16	31-46	6
	PLA_2	NELGRFKMTDACCRTM	30	16	19-34	6
		SKPKVYQWFDLRKY	31	14	115-128	6
	NASE	ATSTKKLHKEPATLIKAIDG	32	20	1-20	6
		PATLIKAIDGDTVKLMYKGQ	33	20	11-30	6
		DRVKLMYKGQPMIFRLLLVD	34	20	21-40	6
		VAYVYKPNNTHEQHLRKSEA	35	20	111-130	6
	HIV p13	QKQEPIDKELYPLTSL	36	16	97-112	6
	HIV p17	GARASVLSGGELDKWE	37	16	1-16	6
	Influenza HA	RTLYQNVGTYVSVGTSTLNK	38	20	187-206	6
	Influenza HA	PKYVKQNTLKLAT	24	13	307-319	17
	P. falcip. p190	LKKLVFGYRKPLDNI	39	15	249-263	25
	P. falcip. CS	KMIEQYLKKIKNS	40	13	329-341	27
	Chicken OVA	DVFKELKVHHANENIF	41	16	15-30	6
	DR1 β chain	GDTRPRFLWQLKFECHFFNG	42	20	1-20	28
		TERVRLLERCIYNQEESVRFDS	43	22	21-42	28
		DLLEQRRAAVDTYCRHNYGVGESFT	44	25	66-90	28
	p Cyt c	KAERADLIAYLKQATAK	45	17	88-104	6
	Myelin basic prot.	GRTQDENPVVHFFKNIVTPRTPPP	46	24	75-98	6

Table 3, continued

A PROTEIN SOURCE	PEPTIDE SEQUENCE	SEQ ID NO.	LENGTH	POSITION	REFERENCE
C Influenza Matrix	PLKAEIAQRLEDV	47	13	19-31	6
HIV p17	RGILGQLQPSLQTGSE	48	16	57-72	6
β_2M	IQVYSRHPPENGKPNI	49	16	7-22	6
PLA_2	INTKCYKLEHPVIGCG	50	16	85-100	6
P. falcip. p190	YKLNFYFDLLRAKL	51	14	211-224	25
	IDTLKKNENIKEL	52	13	338-350	25
DR1 β chain	DVGEYRAVTELGRPDAEYWN	53	20	43-62	28
HIV p17	ERFAVNPGLLETSEGC	54	16	41-56	6
HEL	DNYRGYSLGNWVCAAKFESNFTQ	55	23	20-42	6
NASE	EALVRQGLAKVAYVYKPNNT	56	20	101-120	6
HIV p25	PIVQNLQGQMVHQAIS	57	16	1-16	6
	SALSEGATPQDLNTML	58	16	41-56	6
β_2m	SFYILAHIEFTPTETD	59	16	61-76	6
PLA_2	KMYFNLINTKCYKLEH	60	16	79-94	6

TABLE 4

MST/HLA-DR2 BINDING PEPTIES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Pseudo HLA-A2	103-120	VGSDWRFLRGYHQYAYDG	1	18	DR2-3-57	2190.4	2189.0
	103-119	VGSDWRFLRGYHQYAYAD	61	17	DR2-3-57	2133.3	2131.8
	104-119	GSDWRFLRGYHQYAYD	62	16	DR2-3-56	2034.3	2040.4
	103-117	VGSDWRFLRGYHQYA	2	15	DR2-3-56	1855.0	1858.5
	103-116	VGSDWRFLRGYHQY	3	14	DR2-3-56	1784.0	1786.3
	104-117	GSDWRFLRGYHQYA	4	14	DR2-3-55	1755.3	1755.0*
	105-117	SDWRFLRGYHQYA	5	13	DR2-3-56	1698.2	1702.6
Invariant Chain	97-120	LPKPPKPVSKMRMATPLLMQALPM	7	24	DR2-3-70	2676.4	2675.0*
(Ii)	98-120	PKPPKPVSKMRMATPLLMQALPM	10	23	DR2-3-70	2563.2	2562.0*
	99-120	KPPKPVSKMRMATPLLMQALPM	11	22	DR2-3-70	2466.1	2465.0*
	98-119	PKPPKPVSKMRMATPLLMQALP	12	22	DR2-3-66	2432.0	2437.0
	99-119	KPPKPVSKMRMATPLLMQALP	13	21	DR2-3-66	2334.9	2340.0
	100-119	PPKPVSKMRMATPLLMQALP	63	20	DR2-3-70	2206.7	2207.0*
	106-124	KMRMATPLLMQALPMGALP	64	19	DR2-3-71	2070.5	2074.3
	106-120	KMRMATPLLMQALPM	15	15	DR2-3-70	1732.2	1732.0*
HLA-DQ α-chain	97-119	NIVIKRSNSTAATNEVPEVTVFS	158	23	DR2-3-44	2476.8	2478.1
	97-112	NIVIKRSNSTAATNEV	159	16	DR2-3-41	1716.9	1717.0
HLA-DQ β-chain	42-59	SDVGVYRAVTPQGRPDAE	160	18	DR2-3-41	1917.1	1920.5
	43-59	DVGVYRAVTPQGRPDAE	161	17	DR2-3-41	1830.0	1833.3
	43-57	DVGVYRAVTPQGRPD	162	15	DR2-3-41	1629.8	1632.9
HLA-DR α-chain	182-194	APSPLPETTEMVV	163	13	DR2-3-36	1353.5	1362.0
	182-198	APSPLPETTEMVVCALG	164	17	DF2-3-41	1697.9	1701.0
(MET) Kinase-relate trasforming protein	59-81	EMMIFLGATMYIYVLMEEDLQKV	65	23	DR2-3-65	2746.1	2746.6
Guanylate-bind.	434-450	QELQMKYYQVPRKQIQA	66	17	DR2-3-71	2063.4	2074.3
Mannose-bind. prot.	174-193	IQMLIKEEAFLQITDEKTEG	67	20	DR2-3-70	2248.5	2248.0*

Table 4, continued

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Apolipoprotein B-100	1200-1220	FPKSLHTYANILLDRRVPQTD	165	21	DR2-3-61	2484.8	2490.9
	1200-1218	FPKSLHTYANILLDRRVPQ	166	19	DR2-3-61	2268.6	2276.7
Potassium channel prot	173-190	DGILYYYQSGGRLRRPVN	167	18	DR2-3-61	2127.4	2132.6
	173-189	DGILYYYQSGGRLRRPV	168	17	DR2-3-61	2013.3	2018.1
Fibronectin receptor	586-616	LSPINIALNFSLDPQAPVDSHGLRPALHYQ	169	30	DR2-3-61	3307.7	3313.1
Factor VIII	1175-1790	LMDYGMSSSPHVLRNR	170	16	DR2-3-44	1918.2	1921.7
HLA-DR2b β-chain	94-111	RVQPKVTVYPSKTQPLQH	72	18	DR2-3-39	2106.5	2114.
	94-108	RVQPKVTVYPSKTQP	73	15	DR2-3-39	1728.3	1730.6
							ESI-MS*
							MALD-MS

TABLE 5

WT-20/HLA-DR3 NATURALLY PROCESSED PEPTIDES

Protein Source	Position	Sequence	SEQ ID NO.	Length	Fraction	MW	Mass Spec.
Pseudo HLA-A2	103-117	VGSDWRFLRGYHQYA	2	15	DR3-2-63	1855.0	1863.9
HLA-A30	28-?	VDDTQFVRFDSDAASQ...	171	?	DR3-2-55	?	?
HLA-DR α-chain	111-129	PPEVTVLTNSPVELREPNV	172	19	DR3-2-55	2090.4	2093.3
	111-128	PPEVTVLTNSPVELREPN	173	18	DR3-2-55	1991.2	1989.8
HLA-DR β-chain	1-?	GDTRPRFLEYSTSECHFF	79	18	DR3-2-73	?	?
Acetylcholine recept.	289-304	VFLLLLADKVPETSLS	174	16	DR3-2-65	1745.1	1750.1
Glucose-transport	459-474	TFDEIASGFRQGGASQ	175	16	DR3-2-55	1670.8	1672.6
Sodium channel prot.	384-397	YGYTSYDTFSWAFL	176	14	DR3-2-41	1720.8	1720.5
Invariant chain	97-119	LPKPPKPVSKMRMATPLLMQALP	9	23	DR3-2-73	2545.2	2554.0
(Ii)	98-119	PKPPKPVSKMRMATPLLMQALP	12	22	DR3-2-73	2432.0	2441.4
	99-119	KPPKPVSKMRMATPLLMQALP	13	21	DR3-2-73	2334.9	2345.3
	131-149	ATKYGMMTEDHVMHLLQNA	177	19	DR3-2-69	2173.4	2179.3
CD45	1071-1084	GQVKKNNHQEDKIE	178	14	DR3-2-41	1666.8	1667.0
ICAM-2	64-76	LNKILLDEQAQVK	179	13	DR3-2-51/52	1598.9	1602.4
Interferon γ-receptor	128-147	GPPKLDIRKEEKQIMIDIFH	180	21	DR3-2-77	2505.0	2510.3
	128-148	GPPKLDIRKEEKQIMIDIFHP	181	20	DR3-2-77	2407.8	2412.4
IP-30	38-59	SPLQALDFFGNGPPVNYKTGNL	182	22	DR3-2-77	2505.0	2510.3
	38-57	SPLQALDFFGNGPPVNYKTG	183	20	DR3-2-77	2122.4	2126.2
Cytochrome-b5 reduc.	155-172	GKFAIRPDKKSNPIIRTV	184	18	DR3-2-51/52	2040.4	2043.2
EBV membrane antigen GP220	592-606	TGHGARTSTEPTTDY	185	15	DR3-2-41	1593.6	1592.7
EBV tegument protein membrane p140	1395-1407	KELKRQYEKKLRQ	186	13	DR3-2-51/52	1747.1	1749.8

Table 5, continued

Protein Source	Position	Sequence	SEQ ID NO.	Length	Fraction	MW	Mass Spec.
Apolipoprotein B-100 (Human)	1276-1295	NFLKSDGRIKYTLNKNSLK	74	20	DR3-2-63	2352.9	2360.0
	1273-1292	IPDNLFLKSDGRIKYTLNKN	191	20	DR3-2-65	2349.7	2354.6
	1273-1291	IPDNLFLKSDGRIKYTLNK	75	19	DR3-2-63	2235.5	2245.1
	1273-1290	IPDNLFLKSDGRIKYTLN	192	18	DR3-2-65	2107.4	2096.6
	1273-1289	IPDNLFLKSDGRIKYTL	193	17	DR3-2-65	1993.3	2000.8
	1276-1291	NLFLKSDGRIKYTLNK	76	16	DR3-2-60	1910.2	1911.4
	1276-1290	NLFLKSDGRIKYTLN	77	15	DR3-2-60	1782.1	1785.9
	1207-1224	YANILLDRRVPQTDMTF	78	17	DR3-2-63	2053.3	2059.1
	1794-1810	VTTLNSDLKYNALDLTN	194	17	DR3-2-69	1895.1	1896.5
							MALD-MS

TABLE 6

PRIESS/HLA-DR4 NATURALLY PROCESSED PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Ig Kappa Chain	188-208	KHKVYACEVTHQGLSSPVTKS	80	21	DR4-2-45	2299.6	2304.0
C region (Human	188-207	KHKVYACEVTHQGLSSPVTK	81	20	DR4-2-47	2212.5	2213.0
	189-206	HKVYACEVTHQGLSSPVT	82	18	DR4-2-43	1955.5	1952.1
	188-204	KHKVYACEVTHQGLSSP	83	17	DR4-2-45	1883.1	1882.8
	187-203	EKHKVYACEVTHQGLSS	84	17	DR4-2-45	1915.1	1922.5
	188-203	KHKVYACEVTHQGLSS	85	16	DR4-2-54	1787.0	1787.0
	189-204	HKVYACEVTHQGLSSP	86	16	DR4-2-47	1755.0	1767.8
	187-202	EKHKVYACEVTHQGLS	87	16	DR4-2-43	1828.0	1822.8
	188-202	KHKVYACEVTHQGLS	88	15	DR4-2-51	1699.9	1708.3
	189-203	HKVYACEVTHQGLSS	89	15	DR4-2-45	1657.8	1667.0
	187-200	EKHKVYACEVTHQG	90	14	DR4-2-51	1628.8	1632.6
HLA-DR α-chain	182-198	APSPLPETTENVVCALG	91	17	DR4-2-43	1697.9	1700
HLA-A2	28-50	VDDTQFVRFDSDAASQRMEPRAP	195	23	DR4-2-58	2638.6	2641.5
	28-48	VDDTQFVRFDSDAASQRMEPR	92	21	DR4-2-56	2470.6	2472.9
	28-47	VDDTQFVRFDSDAASQRMEP	93	20	DR4-2-59	2314.5	2319.3
	28-46	VDDTQFVRFDSDAASQRME	94	19	DR4-2-54	2217.2	2218.7
	30-48	DTQFVRFDSDAASQRMEPR	95	19	DR4-2-55	2256.4	2263.2
	31-49	TQFVRFDSDAASQRMEPRA	96	19	DR4-2-56	2212.4	2211.5
	28-44	VDDTQFVRFDSDAASQR	97	17	DR4-2-55	1957.0	1963.1
	31-47	TQFVRFDSDAASQRMEP	98	17	DR4-2-56	1985.1	1987.5
	31-45	TQFVRFDSDAASQRM	99	15	DR4-2-54	1758.9	1761.0
	31-42	TQFVRFDSDAAS	100	12	DR4-2-54	1343.4	1343.3
HLA-C	28-50	VDDTQFVRFDSDAASPRGEPRAP	101	23	DR4-2-56	2533.7	2536.7
	31-52	TQFVRFDSDAASPRGEPRAPWV	102	22	DR4-2-54	2489.7	2491.5
	28-48	VDDTQFVRFDSDAASPRGEPR	103	21	DR4-2-54	2365.5	2368.1
	28-47	VDDTQFVRFDSDAASPRGEP	104	20	DR4-2-56	2209.3	2211.5
	28-46	VDDTQFVRFDSDAASPRGE	105	19	DR4-2-56	2112.2	2113.9

Table 6, continued

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
HLA-Cw9	28-45	VDDTQFVRFDSDAASPRG	106	18	DR4-2-56	1983.1	1987.5
	31-48	TQFVRFDSDAASPRGEPR	107	18	DR4-2-52	2036.2	2041.5
	28-44	VDDTQFVRFDSDAASPR	108	17	DR4-2-55	1926.0	1931.7
	30-46	DTQFVRFDSDAASPRGE	109	17	DR4-2-52	1897.9	1901.6
	31-44	TQFVRFDSDAASPR	110	14	DR4-2-52	1596.7	1603.7
	31-42	TQFVRFDSDAAS	111	12	DR4-2-54	1343.4	1343.3
HLA-C	130-150	LRSWTAADTAAQITQRKWEAA	112	21	DR4-2-56	2374.6	2376.4
	129-147	DLRSWTAADTAAQITQRKW	197	19	DR4-2-58	2218.4	2220.1
	130-147	LRSWTAADTAAQITQRKW	198	18	DR4-2-58	2103.3	2105.0
	129-145	DLRSWTAADTAAQITQR	113	17	DR4-2-59	1904.5	1908.7
	129-144	DLRSWTAADTAAQITQ	114	16	DR4-2-59	1747.9	1752.3
	129-143	DLRSWTAADTAAQIT	115	15	DR4-2-59	1619.7	1622.2
HLA-Bw62	129-150	DLSSWTAADTAAQITQRKWEAA	199	22	DR4-2-65	2420.6	2422.7
	129-145	DLSSWTAADTAAQITQR	116	17	DR4-2-60	1834.9	1838.1
	129-146	DLSSWTAADTAAQITQRK	200	18	DR4-2-65	1963.1	1966.3
	129-148	DLSSWTAADTAAQITQRKWE	117	20	DR4-2-66	2278.4	2284.6
VLA-4	229-248	GSLFVYNITTNKYKAFLDKQ	201	20	DR4-2-65	2350.7	2352.6
	229-244	GSLFVYNITTNKYKAF	202	16	DR4-2-65	1866.1	1868.2
PAI-1	261-281	AAPYEKEVPLSALTNILSAQL	203	21	DR4-2-65	2228.5	2229.5
	261-278	AAPYEKEVPLSALTNILS	204	18	DR4-2-65	1916.2	1917.4
Cathepsin C	151-167	YDHNFVKAINADQKSWT	118	17	DR4-2-70	2037.2	2039.6
(Rat Homologue)		I	119			2035.3	
	151-166	YDHNFVKAINADQKSW	120	16	DR4-2-70	1936.1	1937.7
		I	121			1934.2	
Bovine Hemoglobin	26-41	AEALERMFLSFPTTKT	205	16	DR4-2-78	1842.1	1836.1
HLA-DQ3.2 β-chain	24-38	SPEDFVYQFKGMCYF	206	15	DR4-2-78	1861.1	1861.7
HLA-DR β-chain	1-?	GDTRPRFLEQVKHE...	122	14	DR4-2-72	1711.9	
IG Heavy Chain	121-?	GVYFYLQWGRSTLVSVS...	123	(?)	DR4-2-6	?	?
							MALD-MS

TABLE 7

MAMM/HLA-DR7 NATURALLY PROCESSED PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Pseudo HLA-A2	105-124	SDVRFLRGYHQYAYDGKDYI	207	20	DR7-2-61	2553.8	2556.5
	103-120	VGSDVRFLRGYHQYAYDG	1	18	DR7-2-63	2190.4	2194
	103-117	VGSDVRFLRGYHQYA	2	15	DR7-2-63	1855.0	1860
	104-117	GSDVRFLRGYHQYA	208	14	DR7-2-61	1755.9	1760.8
	104-116	GSDVRFLRGYHQY	209	13	DR7-2-61	1684.8	1687.6
	105-117	SDVRFLRGYHQYA	210	13	DR7-2-61	1698.9	1704.1
HLA-A29	234-253	RPAGDGTFQKWASVVVPSGQ	124	20	DR7-2-66	2087.3	2092
	234-249	RPAGDGTFQKWASVVV	125	16	DR7-2-63	1717	1718
	237-258	GDGTFQKWASVVVPSGQEQRYT	126	22	DR7-2-66	2436	2440
	237-254	GDGTFQKWASVVVPSGQE	127	18	DR7-2-66	1892.3	1892
	239-252	GTFQKWASVVVPSG	128	14	DR7-2-66	1462	1465
	239-253	GTFQKWASVVVPSGQ	129	15	DR7-2-66	1718	1721
	239-261	GTFQKWASVVVPSGQEQRYTCHV	130	23	DR7-2-66	2603	2606
HLA-B44	83-99	RETQISKTNTQTYRENL	211	17	DR7-2-35	2082.3	2086.1
	83-98	RETQISKTNTQTYREN	212	16	DR7-2-35	1969.1	1971.1
	83-97	RETQISKTNTQTYRE	213	15	DR7-2-35	1855.0	1857.3
HLA-DR α-chain	101-126	RSNYTPITNPPEVTVLTNSPVELREP	214	26	DR7-2-35	2924.2	2926.9
	58-78	GALANIAVDKANLEIMTKRSN	131	21	DR7-2-66	2229.5	2221
	182-200	APSPLPETTENVVCALGLTV	215	20	DR7-2-42	1912.2	1917.7
HLA-DQ α-chain	179-?	SLQSPITVEWRAQSESAQSKMLSGIGGFVL	216	?	DR7-2-35	?	?
4F2 Cell-surface	318-338	VTQYLNATGNRVCSWSLSQAR	217	21	DR7-2-71	2441.7	2445.1
antigen heavy chain	318-334	VTQYLNATGNRVCSWSL	218	17	DR7-2-71	1999.2	2001.9
LIF receptor	854-866	TSILCYRKREWIK	219	13	DR7-2-35	1696.0	1700.8
Ig kappa chain C reg.	188-201	KHKVYACEVTHQGL	220	14	DR7-2-61	1612.9	1615.6
	188-200	KHKVYACEVTHQG	221	13	DR7-2-61	1498.7	1501.0
Invariant Chain	98-119	PKPPKPVSKMRMATPLLMQALP	12	22	DR7-2-72	2432.0	2436.6
(Ii)	99-119	KPPKPVSKMRMATPLLMQALP	13	21	DR7-2-72	2334.9	2339.7
K channel protein	492-516	GDHYPKTVSGNLVGALCALAGVLTI	222	25	DR7-2-71	2567.1	2567.3

Table 7, continued

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Heat shock cognate 71 KD protein	38-54	TPSYVAFTDTERLIGDA	132	17	DR7-2-69	1856.0	1856.6
				17	DR7-2-72	1856.0	1857.0
	38-52	TPSYVAFTDTERLIG	133	15	DR7-2-69	1669.8	1671.9
Complement C9	465-483	APVLISQKLSPIYNLVPVK	223	19	DR7-2-61	2079.5	2083.9
Thromboxane-A synthase	406-420	PAFRFTREAAQDCEV	224	15	DR7-2-71	1739.9	1743.0
EBV major capsid prot	1264-1282	VPGLYSPCRAFFNKEELL	225	18	DR7-2-54	2082.4	2081.2
	1264-1277	VPGLYSPCRAFFNK	226	14	DR7-2-54	1597.9	1598.6
Apolipoprotein B-100	1586-1608	KVDLTFSKQHALLCSDYQADYES	227	23	DR7-2-54	2660.9	2662.5
	1586-1600	KVDLTFSKQHALLCS	228	15	DR7-2-54	1689.0	1687.7
	1942-1954	FSHDYRGSTSHRL	229	13	DR7-2-42	1562.7	1567.5
	2077-2089	LPKYFEKKRNTII	230	13	DR7-2-61	1650.0	1653.8
							MALD-MS

TABLE 8

Z3.1/HLA-DR8 NATURALLY PROCESSED PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ. ID NO.	LENGTH	FRACTION	MW	MASS SPEC
HLA-DR α-chain	158-180	SETVFLPREDHLFRKFHYLPFLP	231	23	DR8-3-59	2889.3	2889.0
	182-198	APSPLPETTENVVCALG	232	17	DR8-3-41	1697.9	1704.3
HLA-DR β-chain	1-?	GDTRPRFLEYSTGECYFFNGTERV	233	?	DR8-3-75	-	-
HLA-DP β-chain	80-92	RHNYELDEAVTLQ	234	13	DR8-3-76	1587.7	1591.3
LAM Blast-1 with	88-108	DPQSGALYISKVQKEDNSTYI	235	21	DR8-3-54	2543.6	2549.1
N-acetylglucosamine	92-108	GALYISKVQKEDNSTYI	236	17	DR8-3-52	2116.1	2118.0
	129-146	DPVPKPVIKIEKIEDMDD	237	18	DR8-3-57	2081.4	2085.7
	129-143	DPVPKPVIKIEKIED	238	15	DR8-3-57	1720.0	1724.9
Ig kappa chain	63-80	FTFTISRLEPEDFAVYYC	239	18	DR8-3-57	2201.5	2203.6
	63-77	FTFTISRLEPEDFAV	240	15	DR8-3-57	1772.0	1777.0
LAR protein	1302-1316	DPVEMRRLNYQTPG	241	14	DR8-3-76	1675.9	1679.8
LIF receptor	709-726	YQLLRSNIGYIEELAPIV	242	18	DR8-3-66	2108.5	2112.0
IFN-α receptor	271-287	GNHLYKWKQIPDCENVK	243	17	DR8-3-66	2072.4	2075.1
Interleukin-8	169-188	LPFFLFRQAYHPNNSSPVCY	244	20	DR8-3-59	2400.7	2402.5
receptor							
Metalloproteinase	187-214	QAKFFACIKRSDGSCAWYRGAAPPKQEF	245	28	DR8-2-63	3161.6	3164.9
Inhibitor 2							
	187-205	QAKFFACIKRSDGSCAWYR	246	19	DR8-3-63	2235.5	2233.6
Metalloproteinase	101-118	NRSEEFLIAGKLQDGLLH	134	18	DR8-3-66	2040.3	2042.9
Inhibitor 1							
	101-117	SEEFLIAGKLQDGLL	135	16	DR8-3-70	1789.0	1799.9
	103-117	SEEFLIAGKLQDGLL	247	15	DR8-3-72	1632.9	1646.0
	101-112	NRSEEFLIAGKL	248	12	DR8-3-66	1376.6	1381.8
Cathepsin E	89-112	GNFTVIFDTGSSNLWVPSVYCTSP	249	24	DR8-3-59	2662.9	2664.4
Cathepsin S	189-205	TAFGYIIDNKGIDSDAS	68	17	DR8-3-63	1857.9	1857.1
Cystatin SN	41-58	DEYYRRLLRVLRAREQIV	250	18	DR8-3-63	2348.7	2348.0
Tubulin α-1 chain	207-223	EAIYDICRRNLDIERPT	251	17	DR8-3-63	2077.3	2078.3
	207-219	EAIYDICRRNLDI	252	13	DR8-3-63	1593.8	1595.1
Myosin β-heavy chain	1027-1047	NELEKIKKQVEQEKCEIQAAL	253	21	DR8-3-59	2493.9	2494.0
Ca release channel	2614-2623	RPSMLQNLLR	254	10	DR8-3-68	1250.5	1254.8

Table 8, continued

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ. ID NO.	LENGTH	FRACTION	MW	MASS SPEC
CD35	359-380	DDFMGQLLNGRVLFPVNLQLGA	255	22	DR8-3-72	2417.8	2421.3
CD75	106-122	IPRLQKIWKNYLSWNKY	256	17	DR8-3-66	2195.6	2202.1
c-myc transfor. prot.	371-385	KRSFFALRDQIPDL	257	14	DR8-3-68	1706.0	1709.6
K-ras trasnfor. prot.	164-180	RQYRLKKISKEEKTPGC	258	17	DR8-3-54	2064.4	2066.5
Calcitonin receptor (Hum?)	38-53	EPFLYILGKSRVLEAQ	69	16	DR8-3-78	1863.2	1868.4
α-ENOLASE (?)	23-?	AEVYHDVAASEFF...	259	?	DR8-3-54	--	--
Plasminogen activator inhibitor-1	378-396	DRPFLFVVRHNPTGTVLFM	260	19	DR8-3-59	2246.7	2247.1
	133-148	MPMFFRLFRSTVKQVD	261	16	DR8-3-70	2008.4	2116.4
Apolipoprotein B-100	1724-1743	KNIFMFKVNQEGLKLSNDMM	262	20	DR8-3-62	2393.8	2399.4
	1724-1739	KNIFMFKVNQEGLKLS	263	16	DR8-3-57	1902.2	1903.7
	1780-1799	YKQTVSLDIQPYSLVTTLNS	264	20	DR8-3-54	2271.5	2273.7
	2646-2662	STPEFTILNTLHIPSFT	265	17	DR8-3-80	1918.2	1929.4
	2647-2664	TPEFTILNTLHIPSFTID	266	18	DR8-3-80	2059.3	2073.5
	2647-2662	TPEFTILNTLHIPSFT	267	16	DR8-3-80	1831.1	1841.6
	2885-2900	SNTKYFHKLNIPQLDF	268	16	DR8-3-68	1965.2	1969.9
	2072-2088	LPFFKFLPKYFEKKRNT	269	17	DR8-3-75	2203.6	2207.0
	2072-2086	LPFFKFLPKYFEKKR	270	15	DR8-3-76	1988.4	1992.6
	4022-4036	WNFYYSPQSSPDKKL	271	15	DR8-3-59	1860.0	1863.3
Bovine Transferrin	261-281	DVIWELLNHAQEHFGKDKSKE	272	21	DR8-3-76	2523.8	2524.9
	261-275	DVIWELLINHAQEHFG	273	15	DR8-3-78	1808.0	1818.1
	261-273	DVIWELLNHAQEH	196	13	DR8-3-73	1603.8	1608.8
von Willebrand factor	617-636	IALLLMASQEPQRMSRNFVR	190	20	DR8-3-59	2360.8	2359.7
	617-630	IALLLMASQEPQRM	189	14	DR8-3-59	1600.9	1601.3
							MALD-MS

TABLE 9

HOM2/HLA-DR1 NATURALLY PROCESSED PEPTIDES

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	FRACTION	MW	MASS SPEC
Pseudo HLA-A2	103-117	VGSDWRFLRGYHQYA	2	15	H2/DR1-1-64	1855.0	1854.4
	104-117	GSDWRFLRGYHQYA	4	14	H2/DR1-1-63	1755.3	1755.2
Invariant Chain (Ii)	97-120	LPKPPKPVSKMRMATPLLMQALPM	7	24	H2/DR1-1-77	2676.4	2675.9
	98-121	PKPPKPVSKMRMATPLLMQALPMG	8	24	H2/DR1-1-72	2620.2	2619.7
	97-119	LPKPPKPVSKMRMATPLLMQALP	9	23	H2/DR1-1-73	2545.2	2544.5
	98-120	PKPPKPVSKMRMATPLLMQALPM	10	23	H2/DR1-1-75	2563.2	2562.3
	99-120	KPPKPVSKMRMATPLLMQALPM	11	22	H2/DR1-1-75	2466.1	2465.8
	98-119	PKPPKPVSKMRMATPLLMQALP	12	22	H2/DR1-1-72	2432.0	2431.7
	99-119	KPPKPVSKMRMATPLLMQALP	13	21	H2/DR1-1-72	2334.9	2334.2
							ESI-MS

TABLE 10

SUMMARY OF NATURALLY PROCESSED PEPTIDES BOUND TO HLA-DR EXPRESSED IN NORMAL HUMAN SPLEEN

PROTEIN SOURCE	POSITION	SEQUENCE	SEQ ID NO.	LENGTH	MW	MASS SPEC
HLA-DR α-chain	71/133-156	SETVFLPREDHLFRKFHYLPFLPS	140	24	2976	2982
	71/136-156	VFLPREDHLFRKFHYLPFLPS	141	21	2659	2666
	71/136-155	VFLPREDHLFRKFHYLPFLP	142	20	2572	2579
	71/136-151	VFLPREDHLFRKFHYL	143	16	2118	2126
Calgranulin B	33/25-33	KLGHPDTLN	144	9	994	999
	42/88-114	WASHEKMHEGDEGPGHHHKPGLGEGTP	145	27	2915	2927
	43/88-114	WASHEKMHEGDEGPGHHHKPGLGEGTP	146	27	2017	2926
HLA-B51	42/104-121	GPDGRLLRGHNQYDGK	188	16	2017	2023
Kinase C ζ chain (rat)	42/341-446	TLPPFGPQITDDYGLD	70	16	1704	1705
HLA-DR4 β chain	45/129-144	VRWFRNGQEEKTGVVS	71	16	1892	1894
						MALD-MS

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Robert G. Urban
Roman M. Chicz
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(ii) TITLE OF INVENTION: IMMUNOMODULATORY PEPTIDES

(iii) NUMBER OF SEQUENCES: 273

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Fish & Richardson
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(C) CITY: Boston
(D) STATE: Massachusetts
(E) COUNTRY: U.S.A.
(F) ZIP: 02110-2804

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: 3.5" Diskette, 1.44 Mb
(B) COMPUTER: IBM PS/2 Model 50Z or 55SX
(C) OPERATING SYSTEM: MS-DOS (Version 5.0)
(D) SOFTWARE: WordPerfect (Version 5.1)

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 07/925,460
(B) FILING DATE: August 11, 1992

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Clark, Paul T.
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(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Val Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala Tyr
1 5 10 15

Asp Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Val Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Val Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro
1 5 10 15

Leu Leu Met Gln Ala Leu Pro Met Gly
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro
1 5 10 15

Leu Leu Met Gln Ala Leu Pro Met
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu
1 5 10 15

Leu Met Gln Ala Leu Pro Met Gly
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro
1 5 10 15

Leu Leu Met Gln Ala Leu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu
1 5 10 15

Leu Met Gln Ala Leu Pro Met
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu
1 5 10 15

Met Gln Ala Leu Pro Met
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu
1 5 10 15

Leu Met Gln Ala Leu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu
1 5 10 15

Met Gln Ala Leu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu Met
1 5 10 15
Gln Ala Leu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Lys Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Lys Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Ile Pro Ala Asp Leu Arg Ile Ile Ser Ala Asn Gly Cys Lys Val Asp
1 5 10 15
Asn Ser

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Arg Val Glu Tyr His Phe Leu Ser Pro Tyr Val Ser Pro Lys Glu Ser
1 5 10 15

Pro

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Tyr Lys His Thr Leu Asn Gln Ile Asp Ser Val Lys Val Trp Pro Arg
1 5 10 15

Arg Pro Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Tyr Lys His Thr Leu Asn Gln Ile Asp Ser Val Lys Val Trp Pro Arg
1 5 10 15

Arg Pro

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Asp Val Gly Glu Tyr Arg Ala Val Thr Glu Leu Gly Arg Pro Asp Ala
1 5 10 15

Glu Tyr Trp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Glu Pro Gly Glu Pro Glu Phe Lys Tyr Ile Gly Asn Met His Gly
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Tyr Lys His Thr Leu Asn Gln Ile Asp Ser Val Lys Val Trp Pro Arg
1 5 10 15

Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Pro Lys Tyr Val Lys Gln Asn Thr Leu Lys Leu Ala Thr
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Ser Asp Leu Ser Phe Ser Lys Asp Trp Ser Phe Tyr Leu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Lys Val Phe Gly Arg Cys Glu Leu Ala Ala Ala Met Lys Arg His Gly
1 5 10 15

Leu Asp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Arg Asn Arg Cys Lys Gly Thr Asp Val Gln Ala Trp Ile Arg Gly Cys
1 5 10 15

Arg Leu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

His Pro Pro His Ile Glu Ile Gln Met Leu Lys Asn Gly Lys Lys Ile
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Asn Glu Leu Gly Arg Phe Lys His Thr Asp Ala Cys Cys Arg Thr His
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Ser Lys Pro Lys Val Tyr Gln Trp Phe Asp Leu Arg Lys Tyr
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Ala Thr Ser Thr Lys Lys Leu His Lys Glu Pro Ala Thr Leu Ile Lys
1 5 10 15

Ala Ile Asp Gly
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Pro Ala Thr Leu Ile Lys Ala Ile Asp Gly Asp Thr Val Lys Leu Met
1 5 10 15

Tyr Lys Gly Gln
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Asp Arg Val Lys Leu Met Tyr Lys Gly Gln Pro Met Thr Phe Arg Leu
1 5 10 15

Leu Leu Val Asp
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Val Ala Tyr Val Tyr Lys Pro Asn Asn Thr His Glu Gln His Leu Arg
1 5 10 15

Lys Ser Glu Ala
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Thr Ser Leu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Gly Ala Arg Ala Ser Val Leu Ser Gly Gly Glu Leu Asp Lys Trp Glu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Arg Thr Leu Tyr Gln Asn Val Gly Thr Tyr Val Ser Val Gly Thr Ser
1 5 10 15

Thr Leu Asn Lys
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Leu Lys Lys Leu Val Phe Gly Tyr Arg Lys Pro Leu Asp Asn Ile
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

Lys His Ile Glu Gln Tyr Leu Lys Lys Ile Lys Asn Ser
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Asp Val Phe Lys Glu Leu Lys Val His His Ala Asn Glu Asn Ile Phe
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Gly Asp Thr Arg Pro Arg Phe Leu Trp Gln Leu Lys Phe Glu Cys His
1 5 10 15

Phe Phe Asn Gly
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Thr Glu Arg Val Arg Leu Leu Glu Arg Cys Ile Tyr Asn Gln Glu Glu
1 5 10 15

Ser Val Arg Phe Asp Ser
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Asp Leu Leu Glu Gln Arg Arg Ala Ala Val Asp Thr Tyr Cys Arg His
1 5 10 15

Asn Tyr Gly Val Gly Glu Ser Phe Thr
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Lys Ala Glu Arg Ala Asp Leu Ile Ala Tyr Leu Lys Gln Ala Thr Ala
1 5 10 15

Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

Gly Arg Thr Gln Asp Glu Asn Pro Val Val His Phe Phe Lys Asn Ile
1 5 10 15

Val Thr Pro Arg Thr Pro Pro Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Pro Leu Lys Ala Glu Ile Ala Gln Arg Leu Glu Asp Val
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly Ser Glu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Ile Gln Val Tyr Ser Arg His Pro Pro Glu Asn Gly Lys Pro Asn Ile
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Ile Asn Thr Lys Cys Tyr Lys Leu Glu His Pro Val Thr Gly Cys Gly
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Tyr Lys Leu Asn Phe Tyr Phe Asp Leu Leu Arg Ala Lys Leu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Ile Asp Thr Leu Lys Lys Asn Glu Asn Ile Lys Glu Leu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Asp Val Gly Glu Tyr Arg Ala Val Thr Glu Leu Gly Arg Pro Asp Ala
1 5 10 15
Glu Tyr Trp Asn
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser Glu Gly Cys
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Asp Asn Tyr Arg Gly Tyr Ser Leu Gly Asn Trp Val Cys Ala Ala Lys
1 5 10 15

Phe Glu Ser Asn Phe Thr Gln
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Glu Ala Leu Val Arg Gln Gly Leu Ala Lys Val Ala Tyr Val Tyr Lys
1 5 10 15

Pro Asn Asn Thr
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Pro Ile Val Gln Asn Leu Gln Gly Gln Met Val His Gln Ala Ile Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln Asp Leu Asn Thr Met Leu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Ser Phe Tyr Ile Leu Ala His Thr Glu Phe Thr Pro Thr Glu Thr Asp
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Lys Met Tyr Phe Asn Leu Ile Asn Thr Lys Cys Tyr Lys Leu Glu His
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 61:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

Val Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala Tyr
1 5 10 15
Ala Asp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 62:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala Tyr Asp
1 5 10 15
Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 63:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu Met
1 5 10 15

Gln Ala Leu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 64:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

Lys Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met Gly
1 5 10 15

Ala Leu Pro

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 65:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

Glu His His Ile Phe Leu Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn
1 5 10 15

Glu Glu Asp Leu Gln Lys Val
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 66:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

Gln Glu Leu Lys Asn Lys Tyr Tyr Gln Val Pro Arg Lys Gly Ile Gln
1 5 10 15

Ala

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Ile Gln Asn Leu Ile Lys Glu Glu Ala Phe Leu Gly Ile Thr Asp Glu
1 5 10 15

Lys Thr Glu Gly
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 68:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

Thr Ala Phe Gln Tyr Ile Ile Asp Asn Lys Gly Ile Asp Ser Asp Ala
1 5 10 15

Ser

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

Glu Pro Phe Leu Tyr Ile Leu Gly Lys Ser Arg Val Leu Glu Ala Gln
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

Thr Leu Pro Pro Phe Gln Pro Gln Ile Thr Asp Asp Tyr Gly Leu Asp
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

Val Arg Trp Phe Arg Asn Gly Gln Glu Glu Lys Thr Gly Val Val Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

Arg Val Gln Pro Lys Val Thr Val Tyr Pro Ser Lys Thr Gln Pro Leu
1 5 10 15

Gln His

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

Arg Val Gln Pro Lys Val Thr Val Tyr Pro Ser Lys Thr Gln Pro
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 74:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

Asn Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr Leu Asn Lys Asn
1 5 10 15
Ser Leu Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 75:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

Ile Pro Asp Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr
1 5 10 15
Leu Asn Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 76:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr Leu Asn Lys
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 77:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr Leu Asn
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Tyr Ala Asn Ile Leu Leu Asp Arg Arg Val Pro Gln Thr Asp Met Thr
1 5 10 15

Phe

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

Gly Asp Thr Arg Pro Arg Phe Leu Glu Tyr Ser Thr Ser Glu Cys His
1 5 10 15

Phe Phe

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 80:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
1 5 10 15

Pro Val Thr Lys Ser
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 81:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
1 5 10 15

Pro Val Thr Lys
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
1 5 10 15
Val Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
1 5 10 15
Pro

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 84:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
1 5 10 15
Ser

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 85:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 88:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 90:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 91:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

Ala Pro Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu
1 5 10 15

Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10 15

Arg Met Glu Pro Arg
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10 15

Arg Met Glu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 94:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10 15

Arg Met Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met
1 5 10 15

Glu Pro Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 96

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met Glu
1 5 10 15

Pro Arg Ala

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 97:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10 15

Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 98:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met Glu
1 5 10 15

Pro

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 99:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 100:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 101:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro
1 5 10 15

Arg Gly Glu Pro Arg Ala Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 102:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro Arg Gly Glu
1 5 10 15

Pro Arg Ala Pro Trp Val
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 103:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro
1 5 10 15

Arg Gly Glu Pro Arg
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 104:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro
1 5 10 15

Arg Gly Glu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 105:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro
1 5 10 15

Arg Gly Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 106:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro
1 5 10 15

Arg Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 107:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro Arg Gly Glu
1 5 10 15

Pro Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 108:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro
1 5 10 15

Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 109:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro Arg Gly
1 5 10 15

Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 110:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Pro Arg
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 111:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 112:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln Arg
1 5 10 15

Lys Trp Glu Ala Ala
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 113:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln
1 5 10 15

Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 114:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 115:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 116:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln
1 5 10 15

Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 117:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln
1 5 10 15

Arg Lys Trp Glu
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 118:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Asp Gln Lys Ser Trp
1 5 10 15

Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 119:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Asp Ile Lys Ser Trp
1 5 10 15

Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 120:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Asp Gln Lys Ser Trp
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 121:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Ile Gln Lys Ser Trp
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 122:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

Gly Asp Thr Arg Pro Arg Phe Leu Glu Gln Val Lys His Glu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

Gly Val Tyr Phe Tyr Leu Gln Trp Gly Arg Ser Thr Leu Val Ser Val
1 5 10 15

Ser

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val
1 5 10 15

Pro Ser Gly Gln
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 125:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:

Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 126:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

Gly Asp Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly
1 5 10 15

Gln Glu Gln Arg Tyr Thr
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 127:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

Gly Asp Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly
1 5 10 15

Gln Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 128:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 129:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly Gln
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 130:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

Gly Thr Phe Gln Lys Trp Ala Ser Val Val Val Pro Ser Gly Gln Glu
1 5 10 15

Gln Arg Tyr Thr Cys His Val
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 131:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

Gly Ala Leu Ala Asn Ile Ala Val Asp Lys Ala Asn Leu Glu Ile Met
1 5 10 15

Thr Lys Arg Ser Asn
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 132:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:

Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu Arg Leu Ile Gly Asp
1 5 10 15

Ala

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 133:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:

Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu Arg Leu Ile Gly
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 134:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:

Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu Gln Asp Gly Leu Leu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 135:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu Gln Asp Gly Leu Leu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 136:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:

Asp Val Ile Trp Glu Leu Leu Asn His Ala Gln Glu His Phe Gly
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 137:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

Glu Pro Phe Leu Tyr Ile Leu Gly Lys Ser Arg Val Leu Glu Ala Gln
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 138:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

Thr Ala Phe Gln Tyr Ile Ile Asp Asn Lys Gly Ile Asp Ser Asp
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 139:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

Thr Ala Phe Gln Tyr Ile Ile Asp Asn Lys Gly Ile Asp Ser
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 140:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

Ser Glu Thr Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe
1 5 10 15

His Tyr Leu Pro Phe Leu Pro Ser
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 141:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:

Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu
1 5 10 15

Pro Phe Leu Pro Ser
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 142:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu
1 5 10 15

Pro Phe Leu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 143:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143:

Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 144:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:

Lys Leu Gly His Pro Asp Thr Leu Asn Gln Gly Glu Phe Lys Glu Leu
1 5 10 15

Val Arg Lys Asp Leu Gln Asn Phe Leu Lys
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 145:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:

```
Lys Leu Gly His Pro Asp Thr Leu Asn Gln Gly Glu Phe Lys Glu Leu
 1               5                  10                  15

Val Arg Lys Asp Leu Gln Asn Phe
            20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 146:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:

```
Lys Leu Gly His Pro Asp Thr Leu Asn Gln Gly Glu Phe Lys
 1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 147:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 123
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147:

```
ATG GCC ATA AGT GGA GTC CCT GTG CTA GGA TTT TTC ATC ATA GCT GTG          48
Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val
1               5                  10                  15

CTG ATG AGC GCT CAG GAA TCA TGG GCT AAG ATG CGC ATG GCC ACC CCG          96
Leu Met Ser Ala Gln Glu Ser Trp Ala Lys Met Arg Met Ala Thr Pro
            20                  25                  30

CTG CTG ATG CAG GCG CTG CCC ATG TAA                                     123
Leu Leu Met Gln Ala Leu Pro Met
        35                  40
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 148:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 150
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 148:

```
ATG GCC ATA AGT GGA GTC CCT GTG CTA GGA TTT TTC ATC ATA GCT GTG   48
Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val
1               5                  10                  15

CTG ATG AGC GCT CAG GAA TCA TGG GCT CTT CCC AAG CCT CCC AAG CCT   96
Leu Met Ser Ala Gln Glu Ser Trp Ala Leu Pro Lys Pro Pro Lys Pro
            20                  25                  30

GTG AGC AAG ATG CGC ATG GCC ACC CCG CTG CTG ATG CAG GCG CTG CCC   144
Val Ser Lys Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro
        35                  40                  45

ATG TAA                                                          150
Met
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 149:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

```
Thr Gln Phe Val Arg Phe Asp Ser Asp Ala
 1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 150:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 150:

```
Asp Trp Arg Phe Leu Arg Gly Tyr His Gln
 1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 151:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

```
Arg Met Ala Thr Pro Leu Leu Met Gln Ala
 1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 152:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:

Lys Asp Glu Leu
1

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 153:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:

Lys Phe Glu Arg Gln
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 154:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

Gln Arg Glu Phe Lys
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 155:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val
1 5 10 15

Leu Met Ser Ala Gln Glu Ser Trp Ala
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 156:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:

Met Arg Met Ala Thr Pro Leu Leu Met Gln Ala Leu Pro Met
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 157:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:

Met Pro Arg Ser Arg Ala Leu Ile Leu Gly Val Leu Ala Leu Thr Thr
1 5 10 15

Met Leu Ser Leu Cys Gly Gly
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 158:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 158:

Asn Ile Val Ile Lys Arg Ser Asn Ser Thr Ala Ala Thr Asn Glu Val
1 5 10 15

Pro Glu Val Thr Val Phe Ser
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 159:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 159:

Asn Ile Val Ile Lys Arg Ser Asn Ser Thr Ala Ala Thr Asn Glu Val
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 160:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 160:

Ser Asp Val Gly Val Tyr Arg Ala Val Thr Pro Gln Gly Arg Pro Asp
1 5 10 15

Ala Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 161:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 161:

Asp Val Gly Val Tyr Arg Ala Val Thr Pro Gln Gly Arg Pro Asp Ala
1 5 10 15

Glu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 162:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 162:

Asp Val Gly Val Tyr Arg Ala Val Thr Pro Gln Gly Arg Pro Asp
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 163:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 163:

Ala Pro Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 164:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 164:

Ala Pro Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu
1 5 10 15

Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 165:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 165:

Phe Pro Lys Ser Leu His Thr Tyr Ala Asn Ile Leu Leu Asp Arg Arg
1 5 10 15

Val Pro Gln Thr Asp
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 166:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 166:

Phe Pro Lys Ser Leu His Thr Tyr Ala Asn Ile Leu Leu Asp Arg Arg
1 5 10 15

Val Pro Gln

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 167:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 167:

Asp Gly Ile Leu Tyr Tyr Tyr Gln Ser Gly Gly Arg Leu Arg Arg Pro
1 5 10 15

Val Asn

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 168:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 168:

Asp Gly Ile Leu Tyr Tyr Tyr Gln Ser Gly Gly Arg Leu Arg Arg Pro
1 5 10 15

Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 169:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 169:

Leu Ser Pro Ile His Ile Ala Leu Asn Phe Ser Leu Asp Pro Gln Ala
1 5 10 15

Pro Val Asp Ser His Gly Leu Arg Pro Ala Leu His Tyr Gln
20 25 30

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 170:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 170:

Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 171:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 171:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 172:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 172:

Pro Pro Glu Val Thr Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu
1 5 10 15

Pro Asn Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 173:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 173:

Pro Pro Glu Val Thr Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu
1 5 10 15

Pro Asn

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 174:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 174:

Val Phe Leu Leu Leu Leu Ala Asp Lys Val Pro Glu Thr Ser Leu Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 175:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 175:

Thr Phe Asp Glu Ile Ala Ser Gly Phe Arg Gln Gly Gly Ala Ser Gln
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 176:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 176:

Tyr Gly Tyr Thr Ser Tyr Asp Thr Phe Ser Trp Ala Phe Leu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 177:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 177:

Ala Thr Lys Tyr Gly Asn Met Thr Glu Asp His Val Met His Leu Leu
1 5 10 15

Gln Asn Ala

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 178:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 178:

Gly Gln Val Lys Lys Asn Asn His Gln Glu Asp Lys Ile Glu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 179:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 179:

Leu Asn Lys Ile Leu Leu Asp Glu Gln Ala Gln Trp Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 180:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 180:

Gly Pro Pro Lys Leu Asp Ile Arg Lys Glu Glu Lys Gln Ile Met Ile
1 5 10 15

Asp Ile Phe His
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 181:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 181:

Gly Pro Pro Lys Leu Asp Ile Arg Lys Glu Glu Lys Gln Ile Met Ile
1 5 10 15

Asp Ile Phe His Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 182:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:

Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn Gly Pro Pro Val Asn
1 5 10 15

Tyr Lys Thr Gly Asn Leu
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 183:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 183:

Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn Gly Pro Pro Val Asn
1 5 10 15

Tyr Lys Thr Gly
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 184:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 184:

Gly Lys Phe Ala Ile Arg Pro Asp Lys Lys Ser Asn Pro Ile Ile Arg
1 5 10 15

Thr Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 185:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 185:

Thr Gly His Gly Ala Arg Thr Ser Thr Glu Pro Thr Thr Asp Tyr
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 186:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 186:

Lys Glu Leu Lys Arg Gln Tyr Glu Lys Lys Leu Arg Gln
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 187:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 187:

Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 188:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 188:

Gly Pro Asp Gly Arg Leu Leu Arg Gly His Asn Gln Tyr Asp Gly Lys
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 189:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 189:

Ile Ala Leu Leu Leu Met Ala Ser Gln Glu Pro Gln Arg Met
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 190:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 190:

Ile Ala Leu Leu Leu Met Ala Ser Gln Glu Pro Gln Arg Met Ser Arg
1 5 10 15

Asn Phe Val Arg
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 191:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 191:

Ile Pro Asp Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr
1 5 10 15

Leu Asn Lys Asn
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 192:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 192:

Ile Pro Asp Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr
1 5 10 15

Leu Asn

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 193:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 193:

Ile Pro Asp Asn Leu Phe Leu Lys Ser Asp Gly Arg Ile Lys Tyr Thr
1 5 10 15

Leu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 194:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 194:

Val Thr Thr Leu Asn Ser Asp Leu Lys Tyr Asn Ala Leu Asp Leu Thr
1 5 10 15

Asn

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 195:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 195:

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10 15

Arg Met Glu Pro Arg Ala Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 196:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 196:

Asp Val Ile Trp Glu Leu Leu Asn His Ala Gln Glu His
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 197:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 197:

Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln
1 5 10 15

Arg Lys Trp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 198:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 198:

Leu Arg Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln Arg
1 5 10 15

Lys Trp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 199:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 199:

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln
1 5 10 15

Arg Lys Trp Glu Ala Ala
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 200:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 200:

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln
1 5 10 15

Arg Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 201:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 201:

Gly Ser Leu Phe Val Tyr Asn Ile Thr Thr Asn Lys Tyr Lys Ala Phe
1 5 10 15

Leu Asp Lys Gln
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 202:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 202:

Gly Ser Leu Phe Val Tyr Asn Ile Thr Thr Asn Lys Tyr Lys Ala Phe
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 203:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 203:

Ala Ala Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala Leu Thr Asn Ile
1 5 10 15

Leu Ser Ala Gln Leu
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 204:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 204:

Ala Ala Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala Leu Thr Asn Ile
1 5 10 15

Leu Ser

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 205:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 205:

Ala Glu Ala Leu Glu Arg Met Phe Leu Ser Phe Pro Thr Thr Lys Thr
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 206:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 206:

Ser Pro Glu Asp Phe Val Tyr Gln Phe Lys Gly Met Cys Tyr Phe
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 207:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 207:

Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala Tyr Asp Gly
1 5 10 15

Lys Asp Tyr Ile
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 208:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 208:

Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 209:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 209:

Gly Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 210:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 210:

Ser Asp Trp Arg Phe Leu Arg Gly Tyr His Gln Tyr Ala
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 211:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 211:

Arg Glu Thr Gln Ile Ser Lys Thr Asn Thr Gln Thr Tyr Arg Glu Asn
1 5 10 15

Leu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 212:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 212:

Arg Glu Thr Gln Ile Ser Lys Thr Asn Thr Gln Thr Tyr Arg Glu Asn
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 213:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 213:

Arg Glu Thr Gln Ile Ser Lys Thr Asn Thr Gln Thr Tyr Arg Glu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 214:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 214:

Arg Ser Asn Tyr Thr Pro Ile Thr Asn Pro Pro Glu Val Thr Val Leu
1 5 10 15

Thr Asn Ser Pro Val Glu Leu Arg Glu Pro
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 215:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 215:

Ala Pro Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu
1 5 10 15

Gly Leu Thr Val
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 216:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 216:

Ser Leu Gln Ser Pro Ile Thr Val Glu Trp Arg Ala Gln Ser Glu Ser
1 5 10 15

Ala Gln Ser Lys Met Leu Ser Gly Ile Gly Gly Phe Val Leu
20 25 30

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 217:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 217:

Val Thr Gln Tyr Leu Asn Ala Thr Gly Asn Arg Trp Cys Ser Trp Ser
1 5 10 15

Leu Ser Gln Ala Arg
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 218:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 218:

Val Thr Gln Tyr Leu Asn Ala Thr Gly Asn Arg Trp Cys Ser Trp Ser
1 5 10 15

Leu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 219:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 219:

Thr Ser Ile Leu Cys Tyr Arg Lys Arg Glu Trp Ile Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 220:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 220:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 221:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 221:

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 222:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 222:

Gly Asp Met Tyr Pro Lys Thr Trp Ser Gly Met Leu Val Gly Ala Leu
1 5 10 15

Cys Ala Leu Ala Gly Val Leu Thr Ile
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 223:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 223:

Ala Pro Val Leu Ile Ser Gln Lys Leu Ser Pro Ile Tyr Asn Leu Val
1 5 10 15

Pro Val Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 224:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 224:

Pro Ala Phe Arg Phe Thr Arg Glu Ala Ala Gln Asp Cys Glu Val
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 225:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 225:

Val Pro Gly Leu Tyr Ser Pro Cys Arg Ala Phe Phe Asn Lys Glu Glu
1 5 10 15

Leu Leu

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 226:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 226:

Val Pro Gly Leu Tyr Ser Pro Cys Arg Ala Phe Phe Asn Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 227:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 227:

Lys Val Asp Leu Thr Phe Ser Lys Gln His Ala Leu Leu Cys Ser Asp
1 5 10 15

Tyr Gln Ala Asp Tyr Glu Ser
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 228:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 228:

Lys Val Asp Leu Thr Phe Ser Lys Gln His Ala Leu Leu Cys Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 229:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 229:

Phe Ser His Asp Tyr Arg Gly Ser Thr Ser His Arg Leu
1 2 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 230:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 230:

Leu Pro Lys Tyr Phe Glu Lys Lys Arg Asn Thr Ile Ile
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 231:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 231:

Ser Glu Thr Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe
1 5 10 15

His Tyr Leu Pro Phe Leu Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 232:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 232:

Ala Pro Ser Pro Leu Pro Glu Glu Thr Thr Glu Asn Val Val Cys Ala
1 5 10 15

Leu Gly

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 233:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 233:

Gly Asp Thr Arg Pro Arg Phe Leu Glu Tyr Ser Thr Gly Glu Cys Tyr
1 5 10 15

Phe Phe Asn Gly Thr Glu Arg Val
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 234:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 234:

Arg His Asn Tyr Glu Leu Asp Glu Ala Val Thr Leu Gln
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 235:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 235:

Asp Pro Gln Ser Gly Ala Leu Tyr Ile Ser Lys Val Gln Lys Glu Asp
1 5 10 15

Asn Ser Thr Tyr Ile
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 236:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 236:

Gly Ala Leu Tyr Ile Ser Lys Val Gln Lys Glu Asp Asn Ser Thr Tyr
1 5 10 15

Ile

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 237:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 237:

Asp Pro Val Pro Lys Pro Val Ile Lys Ile Glu Lys Ile Glu Asp Met
1 5 10 15

Asp Asp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 238:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 238:

Asp Pro Val Pro Lys Pro Val Ile Lys Ile Glu Lys Ile Glu Asp
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 239:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 239:

Phe Thr Phe Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr
1 5 10 15

Tyr Cys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 240:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 240:

Phe Thr Phe Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 241:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 241:

Asp Pro Val Glu Met Arg Arg Leu Asn Tyr Gln Thr Pro Gly
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 242:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 242:

Tyr Gln Leu Leu Arg Ser Met Ile Gly Tyr Ile Glu Glu Leu Ala Pro
1 5 10 15

Ile Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 243:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 243:

Gly Asn His Leu Tyr Lys Trp Lys Gln Ile Pro Asp Cys Glu Asn Val
1 5 10 15

Lys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 244:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 244:

Leu Pro Phe Phe Leu Phe Arg Gln Ala Tyr His Pro Asn Asn Ser Ser
1 5 10 15

Pro Val Cys Tyr
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 245:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 245:

Gln Ala Lys Phe Phe Ala Cys Ile Lys Arg Ser Asp Gly Ser Cys Ala
1 5 10 15

Trp Tyr Arg Gly Ala Ala Pro Pro Lys Gln Glu Phe
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 246:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 246:

Gln Ala Lys Phe Phe Ala Cys Ile Lys Arg Ser Asp Gly Ser Cys Ala
1 5 10 15

Trp Tyr Arg

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 247:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 247:

Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu Gln Asp Gly Leu Leu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 248:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 248:

Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 249:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 249:

Gln Asn Phe Thr Val Ile Phe Asp Thr Gly Ser Ser Asn Leu Trp Val
1 5 10 15

Pro Ser Val Tyr Cys Thr Ser Pro
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 250:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 250:

Asp Glu Tyr Tyr Arg Arg Leu Leu Arg Val Leu Arg Ala Arg Glu Gln
1 5 10 15

Ile Val

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 251:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 251:

Glu Ala Ile Tyr Asp Ile Cys Arg Arg Asn Leu Asp Ile Glu Arg Pro
1 5 10 15

Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 252:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 252:

Glu Ala Ile Tyr Asp Ile Cys Arg Arg Asn Leu Asp Ile
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 253:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 253:

His Glu Leu Glu Lys Ile Lys Lys Gln Val Glu Gln Glu Lys Cys Glu
1 5 10 15

Ile Gln Ala Ala Leu
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 254:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 254:

Arg Pro Ser Met Leu Gln His Leu Leu Arg
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 255:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 255:

Asp Asp Phe Met Gly Gln Leu Leu Asn Gly Arg Val Leu Phe Pro Val
1 5 10 15

Asn Leu Gln Leu Gly Ala
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 256:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 256:

Ile Pro Arg Leu Gln Lys Ile Trp Lys Asn Tyr Leu Ser Met Asn Lys
1 5 10 15

Tyr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 257:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 257:

Lys Arg Ser Phe Phe Ala Leu Arg Asp Gln Ile Pro Asp Leu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 258:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 258:

Arg Gln Tyr Arg Leu Lys Lys Ile Ser Lys Glu Glu Lys Thr Pro Gly
1 5 10 15

Cys

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 259:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 259:

Ala Glu Val Tyr His Asp Val Ala Ala Ser Glu Phe Phe
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 260:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 260:

Asp Arg Pro Phe Leu Phe Val Val Arg His Asn Pro Thr Gly Thr Val
1 5 10 15

Leu Phe Met

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 261:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 261:

Met Pro His Phe Phe Arg Leu Phe Arg Ser Thr Val Lys Gln Val Asp
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 262:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 262:

Lys Asn Ile Phe His Phe Lys Val Asn Gln Glu Gly Leu Lys Leu Ser
1 5 10 15

Asn Asp Met Met
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 263:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 263:

Lys Asn Ile Phe His Phe Lys Val Asn Gln Glu Gly Leu Lys Leu Ser
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 264:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 264:

Tyr Lys Gln Thr Val Ser Leu Asp Ile Gln Pro Tyr Ser Leu Val Thr
1 5 10 15

Thr Leu Asn Ser
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 265:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 265:

Ser Thr Pro Glu Phe Thr Ile Leu Asn Thr Leu His Ile Pro Ser Phe
1 5 10 15

Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 266:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 266:

Thr Pro Glu Phe Thr Ile Leu Asn Thr Leu His Ile Pro Ser Phe Thr
1 5 10 15

Ile Asp

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 267:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 267:

Thr Pro Glu Phe Thr Ile Leu Asn Thr Leu His Ile Pro Ser Phe Thr
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 268:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 268:

Ser Asn Thr Lys Tyr Phe His Lys Leu Asn Ile Pro Gln Leu Asp Phe
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 269:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 269:

Leu Pro Phe Phe Lys Phe Leu Pro Lys Tyr Phe Glu Lys Lys Arg Asn
1 5 10 15

Thr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 270:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 270:

Leu Pro Phe Phe Lys Phe Leu Pro Lys Tyr Phe Glu Lys Lys Arg
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 271:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 271:

Trp Asn Phe Tyr Tyr Ser Pro Gln Ser Ser Pro Asp Lys Lys Leu
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 272:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 272:

Asp Val Ile Trp Glu Leu Leu Asn His Ala Gln Glu His Phe Gly Lys
1 5 10 15

Asp Lys Ser Lys Glu
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 273:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 273:

Asp Val Ile Trp Glu Leu Leu Ile Asn His Ala Gln Glu His Phe Gly
1 5 10 15

CLAIMS

1. A purified preparation of a peptide consisting essentially of an amino acid sequence identical to that of a segment of a naturally-occurring human protein, said segment being of 10 to 30 residues in length, inclusive, wherein said peptide binds to a human major histocompatibility complex (MHC) class II allotype.

2. The preparation of claim 1, wherein said peptide binds to at least two distinct MHC class II allotypes.

3. The preparation of claim 1, wherein said human protein is HLA-A2, HLA-A29, HLA-A30, HLA-B44, HLA-B51, HLA-Bw62, HLA-C, HLA-DP β-chain, HLA-DQ α-chain, HLA-DQ β-chain, HLA-DQ3.2 β-chain, HLA-DR α-chain, HLA-DR β-chain, HLA-DR4 β-chain, invariant chain (Ii), Ig kappa chain, Ig kappa chain C region, Ig heavy chain, Na^+/K^+ ATPase, potassium channel protein, sodium channel protein, calcium release channel protein, complement C9, glucose-transport protein, CD35, CD45, CD75, vinculin, calgranulin B, kinase C ζ-chain, integrin β-4 gp150, hemoglobin, tubulin α-1 chain, myosin β-heavy chain, α-enolase, transferrin, transferrin receptor, fibronectin receptor α-chain, acetylcholine receptor, interleukin-8 receptor, interferon α-receptor, interferon γ-receptor, calcitonin receptor, LAM (lymphocyte activation marker) Blast-1, LAR (leukocyte antigen-related) protein, LIF (leukemia inhibitory factor) receptor, 4F2 cell-surface antigen (a cell-surface antigen involved in normal and neoplastic growth) heavy chain, cystatin SN, VLA-4 (a cell surface heterodimer in the integrin superfamily of adhesion receptors), PAI-1 (plasminogen activator inhibitor-1), IP-30 (interferon-γ induced protein), ICAM-2, carboxypeptidase E, thromboxane-A synthase, NADH-cytochrome-b5 reductase, c-myc transforming protein, K-ras transforming protein, MET kinase-related

transforming protein, interferon-induced guanylate-binding protein, mannose-binding protein, apolipoprotein B-100, cathepsin C, cathepsin E, cathepsin S, Factor VIII, von Willebrand factor, metalloproteinase inhibitor 1 precursor, metalloproteinase inhibitor 2, plasminogen activator inhibitor-1, or heat shock cognate 71 kD protein.

4. The preparation of claim 1, wherein said human protein is an MHC class I or II molecule.

5. The preparation of claim 1, wherein said segment conforms to the following motif:

at a first reference position (I) at or within 12 residues of the amino terminal residue of said segment, a positively charged residue or a large hydrophobic residue; and

at position I+5, a hydrogen bond donor residue.

6. The preparation of claim 5, wherein said motif comprises a hydrophobic residue at I+9.

7. The preparation of claim 6, wherein said motif additionally comprises, at position I+1 or I-1, a hydrophobic residue.

8. The preparation of claim 1, wherein said segment comprises residues 29-40 (SEQ ID NO: 187) or residues 106-115 (SEQ ID NO: 150) of HLA-A2.

9. The preparation of claim 1, wherein said segment comprises residues 107-116 of Ii (SEQ ID NO: 151).

10. A liposome containing a peptide consisting essentially of an amino acid sequence identical to that of a segment of a naturally-occurring human protein, said segment being of 10 to 30 residues in length, wherein said peptide binds to a human major histocompatibility complex (MHC) class II allotype.

11. An immune-stimulating complex (ISCOM) comprising a peptide consisting essentially of an amino acid sequence identical to that of a segment of a naturally-occurring human protein, said segment being of 10 to 30 residues in length, wherein said peptide binds to a human major histocompatibility complex (MHC) class II allotype.

12. A nucleic acid encoding a polypeptide, said polypeptide comprising a first and a second amino acid sequence linked by a peptide bond, said first sequence being identical to that of a segment of a naturally-occurring human protein, which segment binds to a human MHC class II allotype and is of 10 to 30 residues in length; and said second sequence being a sequence which controls intracellular trafficking of a polypeptide to which it is attached ("trafficking sequence").

13. The nucleic acid of claim 12, wherein said trafficking sequence is KDEL (SEQ ID NO: 152); KFERQ (SEQ ID NO: 153); QREFK (SEQ ID NO: 154); MAISGVPVLGFFIIAVLMSAQESWA (SEQ ID NO: 155); a pentapeptide comprising Q flanked on one side by four residues selected from K, R, D, E, F, I, V, and L; or a signal peptide.

14. A nucleic acid encoding a polypeptide comprising a first and a second amino acid sequence linked by a peptide bond, said first sequence being identical to that

of a segment of a naturally-occurring human protein, which segment binds to a human MHC class II allotype and is of 10 to 30 residues in length; and said second sequence being substantially identical to human Ii.

15. A cell comprising the nucleic acid molecule of claim 14.

16. A method of making a peptide, which method comprises culturing the cell of claim 15 under conditions permitting expression of said peptide from said nucleic acid molecule.

17. The preparation of claim 1, wherein said segment consists essentially of a sequence set forth in any of Tables 1-10.

18. A method of identifying a nonallelically restricted immunomodulating peptide, said method comprising:

(a) fractionating a mixture of peptides eluted from a first MHC class II allotype;

(b) identifying a self peptide from said mixture;

(c) testing whether said self peptide binds to a second MHC class II allotype, said binding being an indication that said self peptide is a nonallelically restricted immunomodulating peptide.

19. A method of identifying a potential immunomodulating peptide, said method comprising:

(a) providing a cell expressing MHC class II molecules on its surface;

(b) introducing into said cell a nucleic acid encoding a candidate peptide;

(c) determining whether the proportion of said class II molecules which are bound to said candidate peptide is increased in the presence of said nucleic acid compared to the proportion bound in the absence of said nucleic acid, said increase being an indication that said candidate peptide is a potential immunomodulating peptide.

20. A method of identifying a potential immunomodulating peptide, said method comprising:

(a) providing a cell expressing MHC class II molecules on its surface;

(b) introducing into said cell a nucleic acid encoding a candidate peptide;

(c) determining whether the level of MHC class II molecules on the surface of said cell is decreased in the presence of said nucleic acid compared to the level of said molecules in the absence of said nucleic acid, said decrease being an indication that said candidate peptide is a potential immunomodulating peptide.

21. A method of identifying a nonallelically restricted immunostimulating peptide, said method comprising:

(a) providing a cell bearing a first MHC class I or class II allotype, said cell being infected with a pathogen;

(b) eluting a mixture of peptides bound to said cell's first MHC allotype;

(c) identifying a candidate peptide from said mixture, said candidate peptide being a fragment of a protein from said pathogen;

(d) testing whether said candidate peptide binds to a second MHC allotype, said binding being an indication that said candidate peptide is a nonallelically restricted immunostimulating peptide.

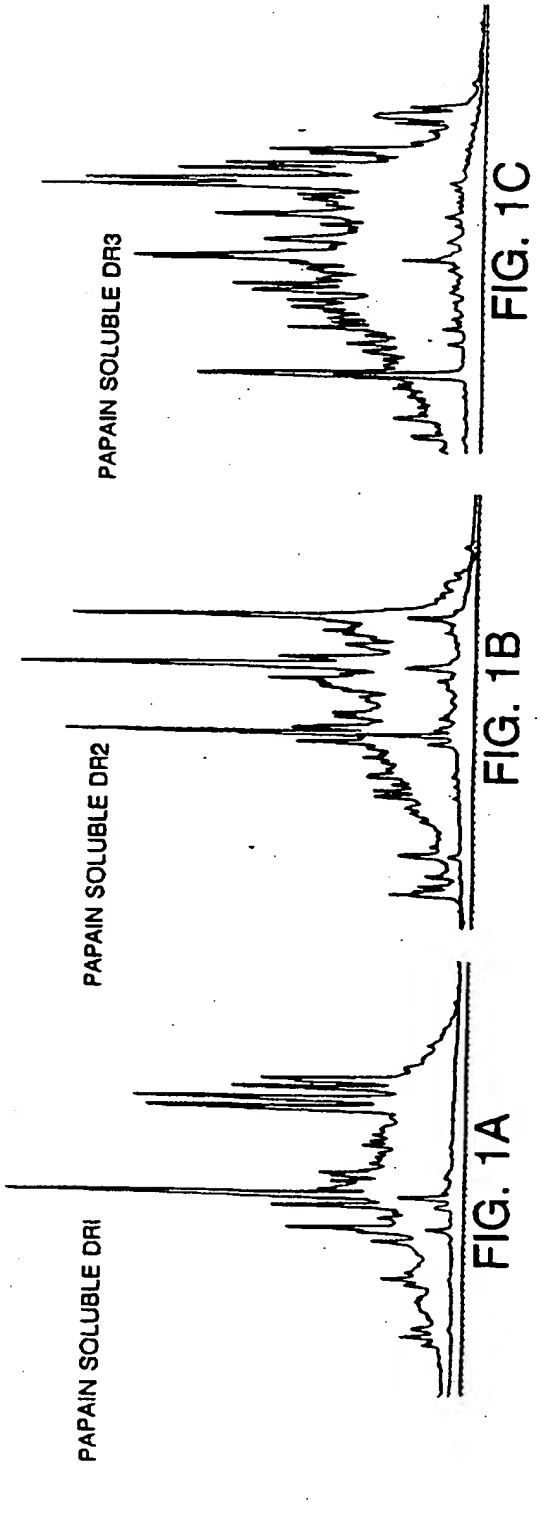

FIG. 1A

FIG. 1B

FIG. 1C

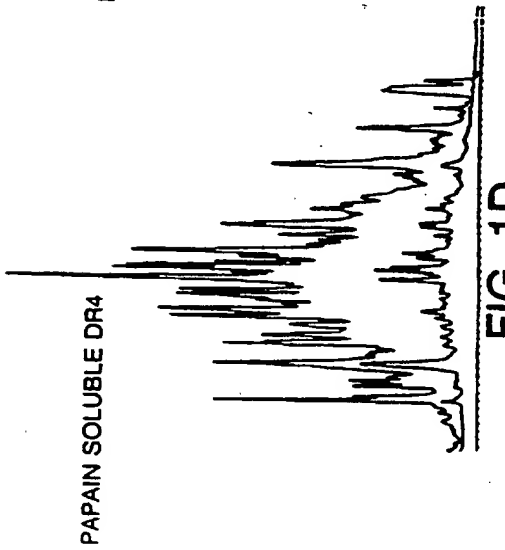

FIG. 1D

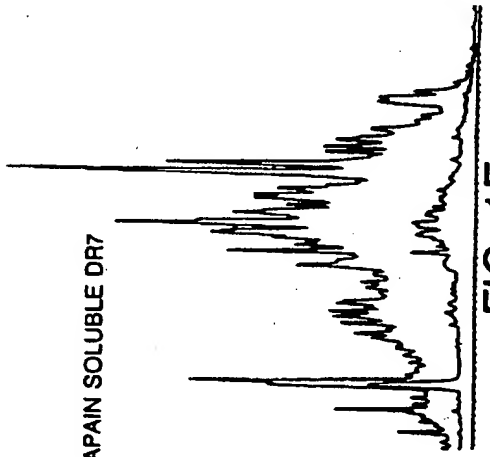

FIG. 1E

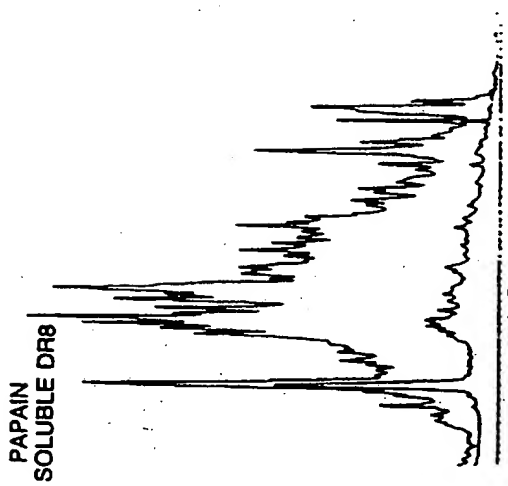

FIG. 1F

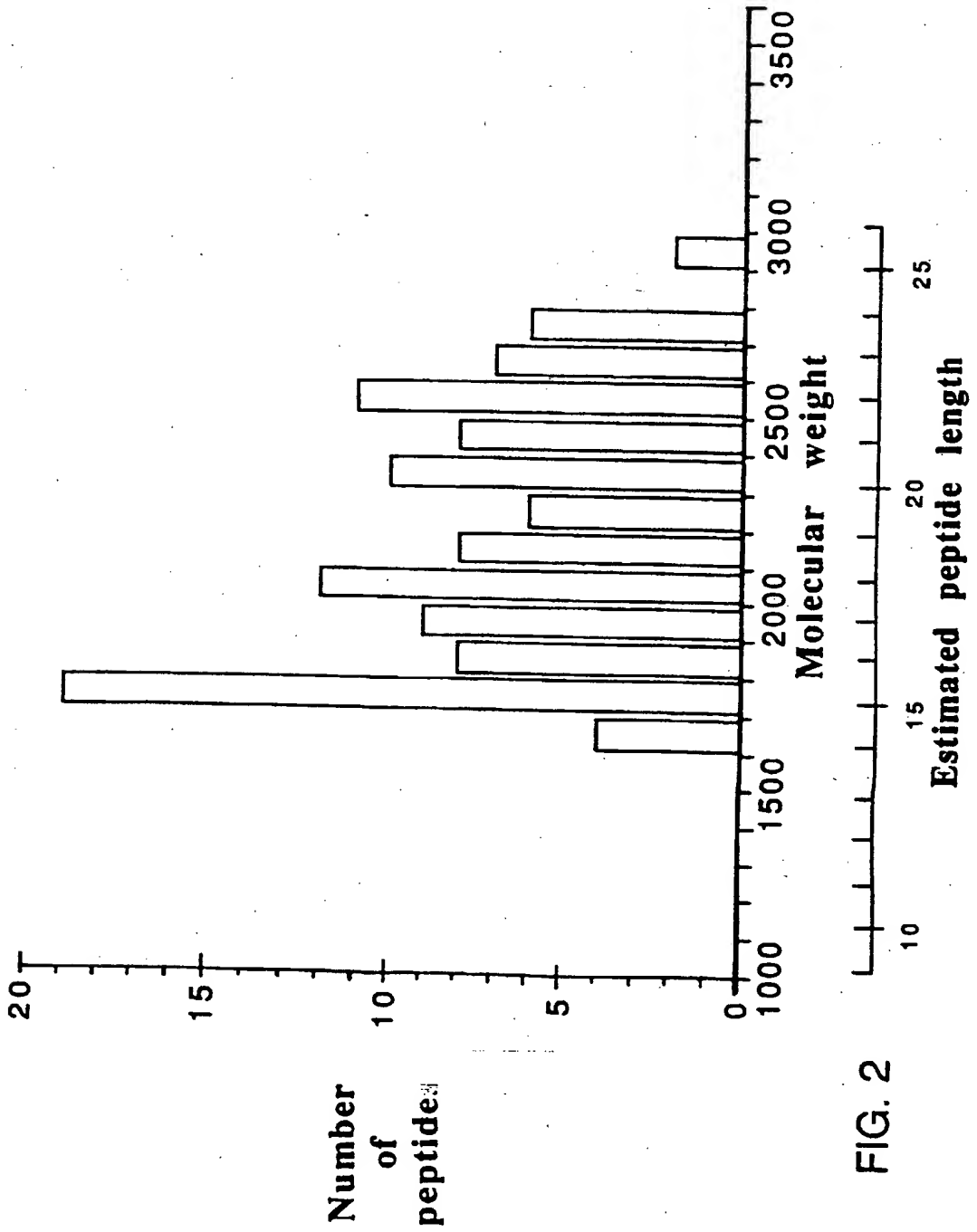
Number of peptides
0
5
10
15
20
1000
1500
2000
2500
3000
3500
Molecular weight
10
15
20
25
Estimated peptide length

FIG. 2

```
ATG GCC ATA AGT GGA GTC CCT GTG CTA GGA TTT TTC ATC ATA GCT
 M   A   I   S   G   V   P   V   L   G   F   F   I   I   A

GTG CTG ATG AGC GCT CAG GAA TCA TGG GCT AAG ATG CGC ATG GCC
 V   L   M   S   A   Q   E   S   W   A   K   M   R   M   A

ACC CCG CTG CTG ATG CAG GCG CTG CCC ATG TAA
 T   P   L   L   M   Q   A   L   P   M  stop
```

FIG. 3A

```
ATG GCC ATA AGT GGA GTC CCT GTG CTA GGA TTT TTC ATC ATA GCT
 M   A   I   S   G   V   P   V   L   G   F   F   I   I   A

GTG CTG ATG AGC GCT CAG GAA TCA TGG GCT CTT CCC AAG CCT CCC
 V   L   M   S   A   Q   E   S   W   A   L   P   K   P   P

AAG CCT GTG AGC AAG ATG CGC ATG GCC ACC CCG CTG CTG ATG CAG
 K   P   V   S   K   M   R   M   A   T   P   L   L   M   Q

GCG CTG CCC ATG TAA
 A   L   P   M  stop
```

FIG. 3B

INTERNATIONAL SEARCH REPORT

L...national application No.
PCT/US93/07545

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 37/00, 37/02, 37/22, 31/70; C07K 7/00, 7/08, 7/10; C07H 17/00
US CL :530/300, 324, 325, 326, 327; 514/2, 44; 536/23.1; 424/450
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/300, 324, 325, 326, 327; 514/2, 44; 536/23.1; 424/450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Medline, Biosis, Chem Abs, Derwent WPI, Embase, search terms: peptide, MHC, class II, DR, I-A, I-E,liposome, iscom, self antigen, author names, antigen presentation, autoimmune

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Immunology, Volume 145, Number 6, Issued 15 September 1990, D.O. Sullivan et al., "Characterization of the specificity of peptide binding to four DR haplotypes", pages 1799-1808, see entire document.	1-18
Y	Immunology Today, Volume 12, Number 11, issued November 1991, A.M. Mowat et al.,"ISCOMS - a novel strategy for mucosal immunization?",pages 383-385, see entire document.	11
Y	Immunology Today, Volume 11, issued January 1990, L. Adorini et al.,"Peptide competition for antigen presentation", pages 21-24, see entire document.	1-18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
07 October 1993	NOV 03 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer RON SCHWADRON Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/07545

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Immunology, Volume 148, issued 01 June 1992, D.S. Collins et al.,"Processing of exogenous liposome encapsulated antigens in vivo generates class I MHC-restricted T cell responses", pages 3336-3341, see entire document..	10

EXHIBIT 2

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
C07K 15/14, A61K 39/385, 39/00	A1	WO 93/14126
		(43) International Publication Date: 22 July 1993 (22.07.93)

(21) International Application Number: PCT/GB93/00102

(22) International Filing Date: 18 January 1993 (18.01.93)

(30) Priority data:
9201023.0 17 January 1992 (17.01.92) GB

(71) Applicant *(for all designated States except US)*: MEDICAL RESEARCH COUNCIL [GB/GB]; 20 Park Crescent, London W1N 4AL (GB).

(72) Inventors; and
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(74) Agents: WOODS, Geoffrey, Corlett et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: A MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II ANTIGEN IN A VACCINE AGAINST AN IMMUNODEFICIENCY VIRUS

(57) Abstract

A major histocompatibility complex class II antigen is useful as a vaccine against an immunodeficiency virus. The antigen may be a human class II antigen such as HLA-DP, HLA-DQ or HLA-DR. The virus may be a human immunodeficiency virus (HIV) such as HIV-1 or HIV-2.

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A MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II ANTIGEN IN A VACCINE AGAINST AN IMMUNODEFICIENCY VIRUS

This invention relates to vaccines against immunodeficiency viruses.

There has been pessimism about the prospects for a successful vaccine against AIDS. The obstacles have often appeared to be insuperable. An effective vaccine must prevent infection by a virus which destroys $CD4^+$ cells, which can integrate into the host DNA and which exhibits rapid antigenic variation. Furthermore, protection must be effective at mucosal surfaces, the primary site of entry, and against both cell-free and cell-associated virus. The simian immunodeficiency virus (SIV)-macaque model, developed in the USA[1,2], was adopted by the United Kingdom MRC AIDS Directed Programme with the primary objective of establishing that vaccination was feasible and that these obstacles to success could be overcome.

We have now demonstrated that a major histocompatibility complex (MHC) class II antigen can protect animals in the SIV-macaque model. Accordingly, the invention provides a class II antigen for use in a method of treatment of the human or animal body by therapy, in particular for use as a vaccine against an immunodeficiency virus.

The invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a MHC class II antigen. The invention further provides use of a MHC class II antigen in the manufacture of a medicament for use as a vaccine against an immunodeficiency virus.

The antigen is preferably a human class II antigen. The antigen may therefore be a HLA-DP, HLA-DQ or HLA-DR antigen such as the HLA-DR4 antigen. These are known antigens and can be obtained in purified form. They may be prepared as recombinant proteins.

Alternatively, the class II antigen may be given presented by transfected cells, i.e. by cells transfected with a gene encoding the antigen and which consequently express the antigen. Transfected cells which may be administered to a human may be transfected cells of a human diploid cell line. Such cell lines have been tested for safety for the purpose of

human vaccine manufacture. An appropriate cell line is the MRC5 cell line.

Allogeneic lymphocytes which present a class II antigen may be administered to a patient. The lymphocytes may be given as live cells, for example as a blood transfusion. Alternatively they may also be given as fixed or inactivated cells. The lymphocytes may be ones in which the expression of the class II antigen has been enhanced, for example by stimulation with a mitogen or gamma-interferon.

The antigen may be used to vaccinate a host against an immunodeficiency virus. The host may be a human or animal but typically it will be wished to vaccinate a human against a human immunodeficiency virus (HIV). That virus may be HIV-1 or HIV-2. A prophylactic treatment for disease states attributable to infection by an immunodeficiency virus can therefore be provided. The class II antigen may in particular act as an AIDS vaccine.

An effective amount of the antigen is administered to a host it is wished to vaccinate. The antigen in whichever form, can be given parenterally, for example subcutaneously, intramuscularly or intravenously. The amount of antigen per dose depends on a variety of factors such as the age and the condition of the subject involved. A parenteral dose typically consists of from 20μg to 1 mg of antigen, for example from 50 to 500 μg of antigen. A number of doses may be given, for example from 2 to 4 doses over a period of up to six months. Each dose may be given one or two months apart.

An agent for use as a vaccine against an immunodeficiency virus is therefore provided. A pharmaceutical composition also comprising a pharmaceutically acceptable carrier or diluent can be formulated. The composition is thus sterile and pyrogen-free. The composition may also comprise an adjuvant such as $Al(OH)_3$ or saponin.

Compositions for intramuscular or subcutaneous injections may contain together with the antigen a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain

as carrier, for example, sterile water or preferably they may be in the form of sterile aqueous isotonic saline solutions.

The MHC class II antigens can be safely used by virtue of their negligible toxicity.

The following Examples illustrate the invention.

Example 1

Inactivated Vaccines

In initial experiments relatively crude, inactivated vaccines were deliberately used (Table 1). The virus infected C8166 cells (Virology, 129, 51-64, 1983 in which the cells are called C63/CR11-2 cells) or partially purified virus, inactivated either by aldehydes or β-propiolactone, were given to groups of three or four cynomolgus macaques. Four doses of vaccine were administered with a rest period of at least six months between the third and final doses. Three different adjuvants were used, either Quil-a (a purified saponin), SAF-1 (Syntex emulsion containing threonyl muramyl di-peptide) or Freund's adjuvant. Each group of vaccinated animals, together with a group of unvaccinated controls, was challenged intravenously with $10MID_{50}$ of the 32H isolate of SIVmac251, two weeks after the final dose of vaccine. All control animals became infected. Virus was repeatedly isolated and proviral DNA detected in peripheral blood lymphocytes after amplification by polymerase chain reaction. Furthermore significant antibody responses to SIV were detected. In contrast there was no evidence of virus infection to any of the vaccinated animals by any of these criteria. These experiments with inactivated virus vaccines have been extended to show that the immunization schedule can be reduced to three doses given at monthly intervals. The duration of protection was assessed by re-challenging animals four to six months after the final dose of vaccine. Five of eight macaques were protected. These results together with other published data[2,3,4,5] demonstrate that inactivated vaccines induce a powerful protection against SIV infection in macaques and that this protection is still detectable at least 6 months after the completion of vaccination.

Cross-Protection

The breadth of protection induced by SIV vaccines

was investigated by vaccinating eight rhesus and eight cynomolgus macaques with formalin inactivated SIV using SAF-1 as adjuvant. Two weeks after the fourth dose of vaccine, four rhesus and four cynomolgus monkeys were challenged with the homologous virus. All eight animals were completely protected against infection. The four remaining rhesus monkeys were challenged with $10MID_{50}$ of $SIV_{deltaB670}$ (kindly supplied by Dr. M. Murphy-Corb). These animals also resisted infection. The remaining four cynomolgus macaques were challenged with $10MID_{50}$ of $HIV\text{-}2_{SBL6669}$ (kindly supplied by Drs. P. Putkonen and G. Biberfield). These animals all became infected. Analysis of the viruses involved in these cross-protection experiments revealed that SIVmac251 and SIV_{delta} share 83% identity in the amino acid sequences of their envelope proteins. In contrast, SIVmac251 and $HIV\text{-}2_{SBL}$ are only 73% identical in the envelope protein. The antigenic diversity of these viruses was established using a panel of 30 monoclonal antibodies made against the envelope protein of SIVmac251. Although all of these antibodies reacted with the vaccine virus in an ELISA assay, 11 failed to react with SIV_{delta} and 20 failed to reach with $HIV\text{-}2_{SBL}$. These results indicate that inactivated vaccine prepared from SIVmac completely protects animals against challenge with the antigenically distinct strain of SIV_{delta}, but that this cross-protection does not extend to the more distantly related HIV-2 virus. Thus, the antigenic variability of immunodeficiency viruses may not be as big an obstacle to successful vaccination as was originally feared. However, this conclusion may require reinterpretation in the light of anti-cell responses discussed below.

Mucosal Immunity

The problem of inducing protection at a mucosal surface was investigated using the intrarectal route of challenge. The standard challenge virus pool of the 32H isolate of SIVmac251, which had been used in all the previous intravenous challenges, was first titrated in rhesus macaques using the intrarectal route. One thousand times more viruses was required to infect monkeys by this route, but the subsequent course of infection was essentially indistinguishable from that following intravenous inoculation.

Four rhesus macaques were then vaccinated subcutaneously with formalin-inactivated SIV using SAF-1 as adjuvant. Two weeks after the fifth dose of vaccine the animals were challenged intrarectally with $10MID_{50}$ based on the intrarectal titration. Four unvaccinated control animals challenged at the same time all became infected. In contrast, all four of the vaccinated animals have remained uninfected over a period of at least six months. This experiment indicates that immunity can be induced against challenge via a mucosal surface.

Challenge with Cell-Associated Virus

A cell associated challenge virus stock was prepared from the spleen of a cynomolgus macaque J82 which had been infected with the 32H isolate of SIVmac251 ten weeks previously. Aliquots of the cells were cryopreserved and then titrated in vitro by co-cultivation with C8166 cells (Table 2). The infectivity titres of the cells and their supernatant fluid were $\log_{10}$ 4.5 and 2.5 respectively. Thus 99% of the infectivity was cell-associated and one ID_{50} was equivalent to 72 viable cells. Subsequent titration of the spleen cells in vivo in monkeys gave an end-point of $\log_{10}$ 3.0 with one ID_{50} being equivalent to 2,300 cells. Having prepared and titrated intravenously an appropriate cell-associated virus challenge, four cynomolus macaques were selected which had previously been vaccinated subcutaneously with inactivated SIV and shown to be protected against intravenous cell-free virus challenge. These animals which had remained free of virus for twelve months following initial challenge were revaccinated and two weeks later challenged intravenously with cell-associated virus (Table 3). The four vaccinated animals, together with four unvaccinated controls, all became infected. Virus and proviral DNA were detected repeatedly in the peripheral blood lymphocytes. Thus a vaccine which had protected against intravenous challenge with cell-free virus grown in a human T-cell line failed to protect against SIV infected simian spleen cells.

Recombinant Vaccines

The specific compounds within the inactivated vaccine which were responsible for the protection were next sought by immunization with a variety of recombinant proteins

derived from SIV genes. Groups of four monkeys were immunised either with p27 expressed on yeast virus-like particles and combined with aluminium hydroxide, or with purified gp160 derived from a recombinant vaccinia virus, or gp130 expressed in CHO cells, or gp140 expressed by baculovirus. Each of the envelope proteins was administered with the Syntex adjuvant formulation. Vaccines were given in four doses and the animals were challenged with $10MID_{50}$ of SIV two weeks after the final dose, together with groups of four unvaccinated control animals. All of these monkeys became infected except one which was vaccinated with the baculovirus derived gp140. Thus although recombinant proteins were able to induce high titres of antibody against SIV envelope, they were not able to protect animals against intravenous challenge.

Immune Correlates of Protection

The immune responses which correlated with protection were analysed by measuring antibody titres in sera taken on the day of challenge from 55 vaccinated macaques used in these studies. Forty three animals had received inactivated vaccines and 12 a recombinant envelope protein (Table 4). Neutralising antibodies were measured against SIVmac251 grown as a persistent infection in HUT-78 cells. The mean titre of neutralizing antibody in the group of 32 macaques which received inactivated vaccine and were protected was $\log_{10}$ 2.0 $\pm$ 0.5. The same mean value was found in the group of 11 animals which were unprotected. Furthermore the 11 animals vaccinated with recombinant envelope proteins and unprotected, had a higher mean titre of $\log_{10}$ 2.9 $\pm$ 0.5. Thus there was no clear correlation between titres of neutralising antibodies and protection in these animals. Titration of these sera against recombinant envelope gp140 by ELISA also failed to show any correlation with protection. Similarly, although these vaccines induced strong T-helper cell proliferation responses to SIV, and in some cases MHC class-II restricted cytotoxic cells, there was no obvious correlation between the cellular responses to SIV and protection. Our failure to find any correlation between the powerful protection we have observed following vaccination and any of the immune responses which we had measured was disturbing. However, it is possible that the

immunological assays we used were inappropriate.

Responses to Cell Components

At this point results of a further vaccine experiment began to emerge which offered explanation for our observations (Table 5). This experiment was originally designed to examine if the two doses of vaccine were sufficient to protect against intravenous challenge with cell-fee virus. Four cynomolgus macaques were vaccinated with SIV-infected C8166 cells using Quil-A as adjuvant at weeks 0 and 4. A control group of four animals were similarly vaccinated but with uninfected C8166 cells. Both groups were challenged with $10MID_{50}$ of virus two weeks after the second dose of vaccine. One of the four animals vaccinated with SIV-infected cells became infected but, surprisingly, only two of the four vaccinated with uninfected cells became infected. In order to confirm these surprising results the protected animals were further vaccinated at week 26 and re-challenged two weeks later together with four naive control macaques. Partial protection was again observed in the animals immunised with uninfected C8166 cells, whereas all four unvaccinated control animals became infected. Antibodies to the cellular component of these vaccines were measured by ELISA using a detergent lysate of C8166 cells as antigen (Table 6). The mean titre of antibody in the eight protected animals was $\log_{10}$ 3.5 and in the five unprotected animals $\log_{10}$ 2.4. The difference between these two groups was highly significant. Analysis of anti-cell antibody levels in all the animals which had received inactivated vaccines showed a similar difference between protected and unprotected animals. Thus there was a statistical correlation between the titre of antibody to C8166 cells and protection in these animals.

Conclusions

These studies demonstrate that at least 3 different inactivated vaccines protect against homologous cell-free SIV. The protection induced is potent since neither virus nor proviral DNA can be detected in the vaccinated animals over prolonged periods following challenge. Five different adjuvants and a variety of immunization procedures are effective. The inactivated vaccines protect against

heterologous challenge with SIV_{delta} but not against HIV-2. The immunity against challenge is reduced but still detectable at four and eight months post-vaccination. Parenteral vaccination with inactivated virus protects against intrarectal challenge with cell-free virus, but not against intravenous challenge with SIV-infected simian spleen cells. Three different preparations of SIV envelope protein were shown to be highly immunogenic, but failed to protect against live intravenous challenge. The protection observed failed to correlate with any of the immune reactions to SIV which were measured. However there was a correlation between protection and levels of antibody to C8166 cells. These results suggest that the protection observed may be mediated at least in part, by immune responses to cellular components present within the inactivated vaccines.

TABLE 1 SUCCESSFUL INACTIVATED SIV VACCINES

VACCINATION		DOSES	OUTCOME OF CHALLENGE*	
ANTIGEN	ADJUVANT	(WEEKS)	CONTROLS	VACCINATES
GLUTARALDEHYDE FIXED SIV-INFECTED CELLS (32H)	QUIL-A	0, 4, 8, 36	4/4	0/4
FORMALDEHYDE FIXED SIV (32H)	SAF-1	0, 4, 8, 32	4/4	0/4
B-PROPIOLACTONE INACTIVATED SIV (BK28)	FREUNDS	0, 4, 8, 39	4/4	0/3

ANIMALS WERE CHALLENGED INTRAVENOUSLY 2 WEEKS AFTER VACCINATION WITH 10 MID_{50}.

* NUMBER INFECTED/NUMBER CHALLENGED

TABLE 2 TITRATION OF CELL ASSOCIATED VIRUS

DILUTION	VIABLE CELLS	INFECTIVITY (NO.INFECT/NO.INOC)		
		CELL CULTURE		MACAQUES
		SUPER	CELLS*	CELLS*
-2	$2.3x10^4$	4/4	4/4	4/4
-3	$2.3x10^3$	0/4	4/4	1/2
-4	$2.3x10^2$	0/4	4/4	0/2
-2	$2.3x10^1$	0/4	0/4	0/2
LOG ID_{50}	-	2.5	4.5	3.0
CELL/ID_{50}	-	-	72	2300

* SPLEEN CELLS FROM SIV-INFECTED CYNO J82

TABLE 3 CHALLENGE WITH CELL-ASSOCIATED SIV

VACCINE	DOSES (WEEKS)	OUTCOME+ NO. INFECT/NO. CHALL
500µG FORMALDEHYDE INACTIVATED SIV + MDP	0, 4, 8, 32 (34)* 83	4/4
GLUTARALDEHYDE INACTIVATED CELLS INFECTED WITH VACC-ENV+GAG + QUIL A	0, 4, 8, 18, 22 41, (43)*, 54	4/4
NONE	-	4/4

* DATE OF INTRAVENOUS CHALLENGE WITH CELL-FREE VIRUS.

\+ ALL ANIMALS CHALLENGED INTRAVENOUSLY WITH INFECTED SPLEEN CELLS TWO WEEKS AFTER LAST DOSE OF VACCINE.

TABLE 4 NEUTRALIZING ANTIBODIES AND PROTECTION

VACCINE	OUTCOME OF CHALLENGE	NO. ANIMALS	ANTIBODY TITRE*	
			MEAN	SD
INACTIVATED	PROTECTED	32	2.0	0.5
	UNPROTECTED	11	2.0	0.4
RECOMBINANT	PROTECTED	1	(3.1)	-
	UNPROTECTED	11	2.9	0.5

* TITRE EXPRESSED AS LOG_{10}

TABLE 5 VACCINATION WITH C8166 CELLS (TRIAL 22)

VACCINE	DOSES (WEEKS)	CHALLENGE	
		WEEK	OUTCOME*
SIV-INFECTED C8166 CELLS + QUIL A	0, 4 26	6 28	1/4 1/3
UNINFECTED C8166 CELLS + QUIL A	0, 4 26	6 28	2/4 1/2
NONE	-	-	4/4

* NO INFECT/NO CHALLENGED

TABLE 6 CORRELATION OF PROTECTION WITH ANTIBODY TO C8166 CELLS

POPULATION	STATUS	No.	ANTIBODY TITRE*			P.
			MEAN	±	SD	
TRIAL 22 (SEE TABLE 5)	PROTECTED	8	3.5	±	0.18	<0.0001
	UNPROTECTED	5	2.4	±	0.20	
ALL ANIMALS GIVEN INACTIVATED VACCINES	PROTECTED	40	3.4		0.56	<0.0001
	UNPROTECTED	15	2.2		0.30	

* TITRES EXPRESSED AS LOG_{10}

Example 2

To confirm the protection influenced by uninfected human T cells, a second experiment was initiated (Table 6). Groups of 4 cynomolgus macaques were vaccinated with either C8166 cells (a human T cell line) or RK-13 cells (rabbit kidney fibroblasts). A third group acted as naive controls. The cells were gently fixed with 0.075% glutaraidehyde and combined with Quil A (a purified saponin) as adjuvant. Each dose comprised 2 x 10^8 cells and 10μg of Quil A. The vaccines were administered subcutaneously at 0, 4, 8 and 16 weeks. Two weeks after the final dose of vaccine all 12 macaques were challenged with 10 monkey infectious doses (MID_{50}) of simian immunodeficiency virus (SIVmac32H) which had been grown in C8166 cells. Virus and proviral DNA was detected in all the control animals and those vaccinated with RK-13 cells but in only two of the four given C8166 cells (Table 2.1).

To confirm and extend this observation the two protected animals were given another dose of C8166 cells at 30 weeks. Two weeks later they, and four naive controls, were challenged with 10 MID_{50} of an antigenically distinct virus, SIVsm3 which had been grown in human peripheral blood mononuclear cells (PBMC) from at least two donors. The controls were all infected but the two vaccinates remained protected.

Finally, the protected animals were vaccinated again at 44 weeks and challenged, together with four controls, with 10 MID_{50} of SIVmac251 grown in simian PBMC. All the animals became infected.

This experiment confirms that uninfected human T cells protect against at least two antigenically distinct strains of SIV grown in human T cells which need not be identical with the cells used as the vaccine. This protection did not extend to SIV grown in simian cells.

Table 6: Uninfected Cell Vaccines

VACCINE	DOSES (WKS)	OUTCOME OF CHALLENGE +		
		1st	2nd	3rd
Uninfected C8166 cells + Quil A	0,4,8,16 30 44	2/4	0/2	2/2
Uninfected RK-13 cells + Quil A	0,4,8,16	4/4	-	-
None	-	4/4		
None			4/4	
None				4/4

+ No. monkeys infected/No. monkeys challenged

Example 3

The major antigens present on the surface of allogeneic or xenogeneic T cells are the major histocompatibility antigens (MHC) class I and class II. To determine if these were responsible for the protection observed groups of four cynomolgus macaques were immunised with either a) normal mouse fibroblasts (L cells), b) L cells (8024 line) transfected with the human genes for MHC class I (HLA B7 + β_2 microglobulin) or c) L cells (8115 line) transfected with the human genes for MHC class II (HLA-DR4). By fluorescent antibody staining, over 90% of 8024 and 8115 cells were expressing class I or class II antigen respectively. The cells were gently fixed in 0.075% glutaraldehyde and combined with 10μg of Quil A as adjuvant (Table 7). Animals were given 2 x 10^6 cells subcutaneously on four occasions at 0,4,8 and 16 weeks. Two weeks after the last dose, all twelve animals were challenged intravenously with 10 MID_{50} of SIVmac32H grown in C8166 cells. All the animals in groups a) and b) became infected but only two of four given cells expressing class II.

This result demonstrates that human MHC class II, namely HLA-DR4, can protect animals against SIV grown in human T cells.

Table 7: MHC Class I or Class II Vaccines

VACCINE	DOSES (WEEKS)	OUTCOME *
a) Normal L cells	0,4,8,16	4/4
b) L cells (8024) expressing class I	0,4,8,16	4/4
c) L cells (8115) expressing class II	0,4,8,16	2/4

* No. monkeys infected/No. monkeys challenged with SIVmac32H.

References

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CLAIMS

1. A major histocompatibility complex class II antigen for use in a method for treatment of the human or animal body by therapy.

2. An antigen according to claim 1 for use as a vaccine against an immunodeficiency virus.

3. An antigen according to claim 2, wherein the virus is human immunodeficiency virus (HIV).

4. An antigen according to claim 3, wherein the virus is HIV-1.

5. An antigen according to claim 3, wherein the virus is HIV-2.

6. An antigen according to any of the preceding claims, which is a human class II antigen.

7. An antigen according to claim 6, which is a HLA-DP, HLA-DQ or HLA-DR antigen.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a major histocompatibility complex class II antigen.

9. Use of a major histocompatibility complex class II antigen in the manufacture of a medicament for use as a vaccine against an immunodeficiency virus.

10. A method of vaccinating a host against an immunodeficiency virus, which method comprising administering to the host an effective amount of a major histocompatibility complex class II antigen.

11. An agent useful as a vaccine against an immunodeficiency virus, which agent comprises a major histocompatibility complex class II antigen.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00102

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K15/14; A61K39/385; A61K39/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category [o]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0 226 513 (INSTITUT PASTEUR) 24 June 1987 see the whole document ---	1-11
X	IMMUNOLOGY LETTERS vol. 24, no. 2, May 1990, AMSTERDAM, THE NETHERLANDS pages 127 - 131 D. LEWIS ET AL. 'HLA-DR peptide inhibits HIV-induced syncytia.' see abstract -----	1-11

[o] Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 APRIL 1993	27.04.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	NOOIJ F.J.M.

INTERNATIONAL SEARCH REPORT

:rnational application No.
PCT/GB93/00102

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of the human /animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300102
SA 68983

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 08/04/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0226513	24-06-87	FR-A- 2591227	12-06-87
		WO-A- 8703601	18-06-87
		JP-T- 63502106	18-08-88